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Developmental Toxicity Potential of Nitroguanidine in Rabbits

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DIVISION OF TOXICOLOGY

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The potential of nitroguanidine to produce developmental toxicity was evaluated in pregnant New Zealand White rabbits. Nitroguanidine, suspended in 1% carboxymethylcellulose, was administered at doses of 0, 100, 316, and 1000 mg/kg/day by oral gavage on Days 6 through 18 of gestation. Fetuses were delivered by cesarean section on Day 29, weighed and examined externally. The soft tissues were examined while the body was being eviscerated for subsequent processing in alizarin red stain for skeletal examination. Ten dams in the 1000-mg/kg/day group died or were terminated in a moribund condition following a generalized failure to thrive. The dams administered 1000 mg/kg/day nitroguanidine exhibited weight loss and decreased food consumption. Signs of developmental toxicity associated with nitroguanidine administration were an increased incidence of resorptions in

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all dose groups. Fetuses in the 1000-mg/kg/day group were lighter in weight and had an increased incidence of retarded ossification of the sternebrae, olecranon, patellae, and phalanges. There were no dose-related malformations. On the basis of these findings, we concluded that nitroguanidine had no teratogenic potential but does have the potential to cause developmental toxicity. Keywords; Teratology; triple base propellants; teratogenic compounds; (KT)

ABSTRACT

The potential of nitroguanidine to produce developmental toxicity was evaluated in pregnant New Zealand White rabbits. Nitroguanidine, suspended in 1% carboxymethylcellulose, was administered at doses of 0, 100, 316, and 1000 mg/kg/day by oral gavage on Days 6 through 18 of gestation. Fetuses were delivered by cesarean section on Day 29, weighed and examined externally. The soft tissues were examined while the body was being eviscerated for subsequent processing in alizarin red stain for skeletal examination. Ten dams in the 1000-mg/kg/day group died or were terminated in a moribund condition following a generalized failure to thrive. The dams administered 1000-mg/kg/day nitroguanidine exhibited weight loss and decreased food consumption. Signs of developmental toxicity associated with nitroguanidine administration were an increased incidence of resorptions in all dose groups. Fetuses in the 1000-mg/kg/day group were lighter in weight and had an increased incidence of retarded ossification of the sternebrae, olecranon, patellae, and phalanges. There were no dose-related malformations. On the basis of these findings, we concluded that nitroguanidine had no teratogenic potential but does have the potential to cause developmental toxicity.

Key Words: Developmental Toxicity, Teratology, Nitroguanidine, Rabbit

PREFACE

TYPE REPORT: Developmental Toxicity Study

TESTING FACILITY: US Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

SPONSOR: US Army Medical Research and Development Command
US Army Biomedical Research and Development Laboratory
Fort Detrick, MD 21701-5010
Project Officer: Gunda Reddy, PhD

PROJECT: 3E162720A835;
Work Unit 180; APC: TLBO

GLP STUDY NUMBER: 86003

STUDY DIRECTOR: Don W. Korte, Jr., PhD, MAJ MSC

PRINCIPAL INVESTIGATOR: Valerie G. Coppes, BS

CO-PRINCIPAL INVESTIGATORS: Charlotte L. Gomez
Dean K. Magnuson, BS, SP4

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocol, SOPs, and raw data will be retained in the LAIR Archives. Alizarin specimens will be retained in the LAIR Pathology Archives.

TEST SUBSTANCE: Nitroguanidine

INCLUSIVE STUDY DATES: 25 September 1986 - 19 February 1987

OBJECTIVE: The purpose of this study was to determine the developmental toxicity potential of nitroguanidine in pregnant New Zealand White rabbits when administered orally during the period of organogenesis.

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SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 86003 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte 26 Sep 88
DON W. KORTE JR., PhD / DATE
MAJ, MSC
Study Director

Dean K. Magnuson 26 Sep 88
DEAN K. MAGNUSON, BS / DATE
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DEPARTMENT OF THE ARMY

LETTERMAN ARMY INSTITUTE OF RESEARCH
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REPLY TO
ATTENTION OF:

SGRD-ULZ-QA

23 September 1988

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance Statement

1. This is to certify that the protocol for GLP Study 86003 was reviewed on 16 July 1986.

2. The institute report entitled "Developmental Toxicity Potential of Nitroguanidine in Rabbits," Toxicology Series 184, was audited on 12 August 1988.

Carolyn M. Lewis

CAROLYN M. LEWIS
Chief, Quality Assurance

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INTRODUCTION

Nitroguanidine, a primary component of US Army triple-base propellants, is now produced in a Government-owned contractor-operated ammunition plant. The US Army Biomedical Research and Development Laboratory (USABRDL), as part of its mission to evaluate the environmental and health hazards of military-unique pollutants generated by US Army munitions-manufacturing facilities, conducted a review of the nitroguanidine data base and identified significant gaps in the toxicity data (1). The Division of Toxicology, LAIR, was tasked by USABRDL to develop a genetic and mammalian toxicity profile for nitroguanidine, related intermediates/by-products of its manufacture, and its environmental degradation products. The rabbit developmental toxicity study described in this report represented one of three studies (a rat developmental toxicity study and rat multigeneration reproductive study are the others) in the reproductive toxicity assessment being conducted as part of the health effects profile of nitroguanidine.

Objective of the Study

The purpose of this study was to determine the developmental toxicity potential of nitroguanidine in pregnant New Zealand White rabbits when administered orally during the period of organogenesis.

MATERIALS

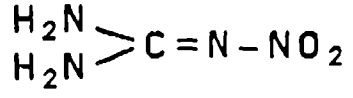
Test Substance

Chemical Name: Nitroguanidine

Chemical Abstracts Service Registry No.: 556-88-7

Toxicology Group Test Compound No.: Phase I TP036A
Phase II TP036B

Molecular Structure



Source: Hercules Aerospace Division
Sunflower Ammunition Plant
DeSoto, Kansas

Lot No.: Phase I SOW84K010-A-001
Phase II SOW85F011-028

Molecular Weight: 104.1

Physical State: White powder

Other test substance information is presented in Appendix A.

Vehicle

The vehicle for nitroguanidine was a 1% solution of carboxymethylcellulose sodium salt, high viscosity (Sigma Chemical Co., St. Louis, MO). Nitroguanidine is not soluble in water at the concentrations tested. Carboxymethylcellulose holds nitroguanidine in a homogeneous suspension.

Animal Data

New Zealand White rabbits were obtained from Elkhorn Rabbitry, Watsonville, CA. The study was conducted in two phases due to the number of animals required. Seventy-eight nulliparous females, approximately 4 months of age upon arrival at LAIR, and eighteen proven breeder males were used. Animals were identified individually by ear tattoo numbers. Additional animal data are presented in Appendix B.

A positive control study with hydroxyurea established the New Zealand White rabbit as a sensitive test system for developmental toxicity studies at LAIR (2). Historic data on malformations and variants in New Zealand White rabbits are well documented (3-5).

Husbandry

Rabbits were housed individually in stainless steel wire mesh cages with automatic water dispensers. Bedding was not provided. Animals were fed Purina Certified Rabbit Chow 5322 (Ralston Purina Company, St. Louis, MO). Males and nonbred females were fed approximately 150 g per day; bred females were given 300 g per day, and their feed consumption was monitored. Water (reverse osmosis Technic Central Systems, Series 300) was available *ad libitum* throughout the study. No contaminants or naturally occurring substances were expected to influence the study. The animal room temperature ranged between 14°C and 21°C, and the relative humidity ranged between 42 and 78 percent (range of hygrothermograph

readings recorded in daily room log). The photoperiod was 12 hours of light per day.

METHODS

Methods used are described in detail in OP-STX-40 "Developmental Toxicity Study" (5) and were in accordance with Environmental Protection Agency Good Laboratory Practice Standards (6) and Health Effects Testing Guidelines (7).

Acclimation

Animals were acclimatized for approximately three weeks prior to start of breeding.

Group Assignment

Females were assigned to test groups by the weight-biased, stratified randomization method (OP-STX-78 "Stratified Randomization"), which is based on the body weight at the start of breeding (8), on the Data General Eagle MV8000 computer.

Dose Levels

Dose levels tested were 0, 100, 316, and 1000 mg/kg/day. Bred females were dosed daily from Day 6 through Day 18 of gestation by oral intubation using a syringe equipped with a 13-cm length of endotracheal catheter tubing. Dosing was conducted without sedation or anesthetization of the animals. The dose for each female was based on the Day 6 body weight, and that dose was used throughout the treatment period. Phase I females were dosed from 20 Oct 86 through 15 Nov 86. Phase II females were dosed from 18 Jan 87 through 8 Feb 87.

Compound Preparation and Analysis

Initially, a smooth paste containing nitroguanidine and a small amount of vehicle was prepared in a mortar with a pestle. Vehicle was then added gradually until the final volume was obtained. The concentrations prepared were 20 mg/ml for the 100-mg/kg/day dose, 63.2 mg/ml for the 316-mg/kg/day dose, and 200 mg/ml for the 1000-mg/kg/day dose. The dosing suspensions and vehicle control were given at a volume of 5 ml/kg body weight. The vehicle and dosing suspensions were prepared prior to the start of dosing for each study phase and refrigerated. Before the animals were dosed each day, the containers of dosing preparation were placed in a beaker of hot tap water for 15 to 30 minutes to bring the suspensions to room temperature. Chemical analyses for accuracy and homogeneity of the dosing suspensions are reported in Appendix C.

Breeding

Each female was bred randomly to two males. Mating was confirmed by observation of the pair mating. Immediately after the first mating, the female was removed from the male's cage and placed with another male. After the second mating the bred female was returned to her cage. Day 0 for each female was the day of mating.

Cesarean Section Procedure

Dams were weighed and euthanized with sodium pentobarbital overdose administered i.v. on Day 29 of gestation. All females were examined, and nonpregnant ones were removed from the study. Gravid uteri were examined for implantations (resorptions and live and dead fetuses). Each implantation was assigned an identification letter. The fetuses, uterus, and ovaries were removed, the corpora lutea were counted, and the dam was examined for gross visceral signs of toxicity and reweighed. Each fetus was weighed, measured crown-to-rump, and examined externally.

Fetuses were placed in 70% ethanol and then carefully eviscerated. The viscera were examined for anomalies, and the sex of the fetus was determined. The fetuses were then processed by the alizarin red S staining technique of Crary (9). After processing, the specimens were stored in glycerol with a few crystals of thymol to inhibit bacterial and mold growth.

Observations and Records

Bred females were weighed on Days 0, 6, 12, 18, 23, and 29. Their feed was weighed, and food consumption was calculated daily. Females were observed daily from Day 0 through Day 29 for clinical signs of toxicity, abortion, or premature delivery. Date, time, and volume of dosing suspension administered were recorded during the daily dosing on Days 6 through 18. At cesarean section, uterine data, gravid body weight, number of corpora lutea, and results from gross examination of the dam were recorded. Dams were reweighed after the removal of the gravid uterus to determine the "Corrected Day 29" weight.

Fetal weight, crown-to-rump measurement, and external examination findings from live fetuses were recorded. Visceral examination findings and sex were recorded. The skeletons stained by alizarin were examined under low magnification on a light box for malformations, alignment, and degree of ossification. The ossified sternebrae, ribs, caudal vertebrae, metacarpals, metatarsals, and phalanges were counted.

Schedule of Study Events

The study was divided into two phases to allow adequate time for animal care, fetal processing, and fetal examination. The historical listing of study events is given in Appendix D.

Statistical Analysis

The data were analyzed with BMDP software on a Data General Eagle MV8000 computer (10). Methods used are described by Winer (11). Data from both phases were combined for analysis. The litter or litter mean was used as the experimental unit. All tests were run at the 0.05 level of significance. The maternal body weights, weight changes, food consumption, and fetal weights and lengths were compared by one-way analysis of variance. Then, if a significant F value occurred, the Newman-Keuls test was applied to the data. The implantation efficiency, percent resorptions, and percent live and dead fetuses were compared by the nonparametric Kruskal-Wallis test. If the Kruskal-Wallis test was significant, an appropriate multiple comparison test was used to determine which groups were different (12). The numbers of litters per group with resorptions, litters with dead fetuses, litters containing fetuses with skeletal or any variations, and the number of fetuses with skeletal or any variations were compared by chi-square analysis, and, if these were significant, the Marascuilo's method of multiple comparison was used to determine which groups were different (13). The numbers of fetuses or litters with malformations or external or visceral variations were not compared statistically because there were too few.

Changes/Deviations

The study was accomplished according to the protocol and addenda.

Raw Data and Final Report Storage

A copy of the final report, study protocol, addenda, raw data, SOPs, and an aliquot of test compound will be retained in the LAIR Archives. Alizarin specimens will be retained in the LAIR Pathology Archives.

RESULTS

Maternal Data

The number of sperm-positive females in each group, number of animals that died during the study, and number of

animals that were pregnant are presented in Table 1. Nitroguanidine did not affect the pregnancy rate. The number of litters with resorptions was significantly higher in the 100-mg/kg/day and the 1000-mg/kg/day groups in comparison to the control group. The 316-mg/kg/day group also had an increased number of litters with resorptions, but the number of litters was not significant in comparison to the control group.

Six animals from the 1000-mg/kg/day group died during the study.

- 86F216, found dead on Day 14, lost 988 g body weight from Day 6 to Day 14 and had thick, foamy, granular orange-rust colored urine, convulsions, hypertonia, loss of consciousness, shallow, rapid respiration, dehydration, and mucus in the nose during the treatment period. Necropsy findings included congestion of the lungs and liver and severe lymphoid depletion of the thymus and spleen.

- 86F229, found dead on Day 11, lost 812 g body weight from Day 6 to Day 11, had orange-rust colored urine, was prostrate following convulsions, moved stiffly, had red material in urine during the treatment period, and had a ruptured stomach at necropsy.

- 86F233, found dead on Day 19, lost 359 g body weight from Day 6 to Day 18, and clinical signs observed included thick, foamy, orange-rust colored urine, convulsions, tremors, and prostration. Necropsy findings included biliary hyperplasia of the lung and slight multifocal hemorrhage in the brain and lung.

- 86F315 lost 674 g from Day 6 to Day 11, had thick, foamy, orange-rust colored urine, hunched posture, hypertonia, was inactive and cool to the touch, and was found dead on Day 11. Necropsy findings were meningoencephalitis of the cerebrum and cerebellum and granulomas of the liver.

- Clinical signs for animal 86F319, found dead on Day 15, were weight loss of 815 g from Day 6 to Day 15, thick, foamy urine, red-stained nose and mouth, and hypertonia. Necropsy findings were renal mineralization, two masses of congealed dosing material in the pyloric area of the stomach, and an esophageal rupture at the thoracic inlet.

- Animal 86F306, found dead on Day 11, had lost 857 g from Day 6 to Day 10, moved stiffly, and had thick, foamy, orange-rust colored urine, hunched posture, and cyanosis. Congestion of the lungs was noted at necropsy. Pregnancy status was not reported for this animal.

Four moribund animals from the 1000-mg/kg/day group were euthanized during the study.

- Animal 86F209, euthanized on Day 12, had a weight loss of 967 g from Day 6 to Day 12, granular, foamy red urine, red nasal discharge, red-stained hindquarters, hunched posture, and tremors, and it moved stiffly. A bloody hairball was found under the cage on Day 12. Morphologic diagnosis for this pregnant animal was acute, multifocal placentitis.

- 86F293, euthanized on Day 16, had a weight loss of 538 g from Day 6 to Day 16, thick, foamy, orange-rust colored urine from Days 6 through 13 but clear yellow urine on Day 14, hunched posture, hypertonia, convulsions, cyanosis, and ataxia. Necropsy of this pregnant animal revealed mild vasculitis of the cerebral choroid plexus.

- 86F286, euthanized on Day 9, lost 599 g body weight from Day 6 to Day 9, moved stiffly, and had thick, foamy urine, red material in urine, red-stained hindquarters, hunched posture, and tremors. A bloody hairball was found under the cage. At necropsy this bred animal was not pregnant and revealed nephrosis.

- 86F318, also euthanized on Day 16, lost 571 g body weight from Day 6 to Day 16 and had thick, foamy, orange-rust colored urine and convulsions. Necropsy findings on this animal were hyperplasia of the bile duct and vacuolar change and hepatocellular loss in the liver. Pregnancy status was not reported for this animal.

Clinical signs, body weights, and food consumption of animals not pregnant at necropsy or cesarean section or of the two animals whose pregnancy status was not included in the necropsy results are not included in this report.

Individual maternal body weights and average daily food consumption for the pretreatment, treatment, and posttreatment study periods are presented in Appendix E and Appendix F, respectively. Results of maternal body weights,

weight changes, and food consumption by group are in Table 2. When given at 1000 mg/kg/day, nitroguanidine produced significant weight loss and decreased food consumption during the treatment period, Days 6 to 18, in comparison to the controls. Lower doses of nitroguanidine did not significantly affect maternal weight gain or food consumption, although there was a trend toward reduced body weight gain with increasing dose from Days 6 to 18.

Individual maternal clinical signs are listed in Appendix G. Summaries of clinical signs by dose group during the pretreatment (Day 0 through Day 5), treatment (Day 6 through Day 18),and posttreatment (Day 19 through Day 29) periods are found in Tables 3a, 3b, and 3c, respectively. Dose-related clinical signs, which occurred with a high frequency in the 1000-mg/kg/day group during the treatment period, included orange-rust colored urine which was often thick and foamy and decreased amount of feces found under the cage. Clinical signs occurring only in the 1000-mg/kg/day group included hunched posture, hypertonia, increased startle reflex, and death or moribund condition.

Individual maternal gross necropsy findings at cesarean section are listed in Appendix H, and a summary by group is found in Table 4. Findings were observed in all dose groups. Cysts on fallopian tubes or dark red fallopian tubes were observed most frequently.

Cesarean/Fetal Data

The individual gestational data are listed in Appendix I, the mean gestational data by group in Table 5. Nitroguanidine had no effect on the number of corpora lutea, implantations, and live and dead fetuses. Percent resorption was significantly increased in all nitroguanidine dose groups in comparison to the control.

The number of live males and females per litter and the average fetal weight and length per litter are given in Appendix J; the group means are in Table 6. Nitroguanidine did not affect the male-to-female ratio. Male and female fetuses from the 1000-mg/kg/day dose group were significantly lighter in weight than the controls. There was no size difference in the 100- and 316-mg/kg/day dose group fetuses in comparison to the controls.

Individual external examination findings are presented in Appendix K. A summary by dose group is in Table 7. The only variation observed was bloated abdomen in one fetus in the 1000-mg/kg/day group. Malformations observed were hindpaw ectrodactyly in one 100-mg/kg/day fetus and cleft palate in one 1000-mg/kg/day fetus.

Individual visceral examination findings are in Appendix L, and a summary by dose group is presented in Table 8. Visceral variations occurred in four fetuses. Dilated renal pelvis occurred in one fetus in the 100-mg/kg/day group and in one fetus in the 316-mg/kg/day group. Elongated ovaries occurred in one 316-mg/kg/day fetus. Enlarged left ventricle of the heart occurred in one 1000-mg/kg/day fetus. The 1000-mg/kg/day fetus with the cleft palate at the external examination also had the only visceral malformation in the study. The left ureter transversed the midline and ran adjacent to the right ureter.

Individual skeletal variations and malformations are described in Appendix M, and a group summary appears in Table 9. Skeletal variations occurred in all dose groups. There was no difference in the number of litters containing fetuses with variations, but the number of fetuses with variations in the 1000-mg/kg/day group was significantly higher in comparison to the control group. Variants most frequently seen were reduced ossification of the sternebrae, olecranon, patellae, and phalanges. The only two skeletal malformations were observed in the fetus with ectrodactyly in the 100-mg/kg/day group and in the fetus with cleft palate in the 1000-mg/kg/day group previously described as external malformations. Skeletal examination of the fetus with ectrodactyly revealed one metatarsal and four phalanges absent from the right hindpaw, one metatarsal and seven phalanges absent from the left, and the three phalanges of the left forepaw pollex absent.

The individual incidence of external, visceral, and skeletal variations and malformations is found in Appendix N, and the individual incidence of any variation and malformation is found in Appendix O. A summary by dose group of the effect of nitroguanidine on the incidence of fetal malformations and variations is presented in Table 10. There was no significant difference in the rate of malformations among the dose groups. The number of fetuses with skeletal variations was significantly increased in the 1000-mg/kg/day dose group in comparison to the control.

TABLE 1

Effect of Nitroguanidine on
Survival and Pregnancy

Examination Finding	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Bred females	17	18	16	22
Females that died*	0	0	0	10
Nongravid	0	0	0	1
Gravid	0	0	0	7
Pregnancy not confirmed	0	0	0	2
Females examined on Day 29	17	18	16	12
Nongravid	4	3	1	1
Gravid	13	15	15	11
With live fetuses	13	15	15	10
With dead fetuses	0	3	1	2
With resorptions	3	13†	7	5†
Resorptions only	0	0	0	1
Females that were gravid	13	15	15	18

*Includes females that were euthanized in a moribund condition.
†Significantly different from control by Marascuilo's method of multiple comparison of proportions, $p < 0.05$.

TABLE 2

Effect of Nitroguanidine on Maternal
Body Weight Changes and Average Food Consumption*

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Average body weight (kg)				
Day 0	3.80 ± 0.27	3.74 ± 0.31	3.76 ± 0.28	3.66 ± 0.19
Day 6	4.04 ± 0.28	4.04 ± 0.39	4.05 ± 0.29	4.01 ± 0.21
Day 18	4.29 ± 0.30	4.26 ± 0.40	4.22 ± 0.30	3.98 ± 0.37
Day 29 Gravid	4.51 ± 0.41	4.49 ± 0.50	4.50 ± 0.33	4.38 ± 0.40
Day 29 Corrected	4.00 ± 0.39	4.02 ± 0.45	4.04 ± 0.29	4.01 ± 0.25
Weight change (kg)				
Days Corrected 29 - 0	0.21 ± 0.38	0.28 ± 0.23	0.28 ± 0.16	0.25 ± 0.25
Days 18 - 6	0.26 ± 0.23	0.23 ± 0.11	0.18 ± 0.11	-0.10 ± 0.28†
Average daily food consumption (g)				
Days 0 - 6	235 ± 20	240 ± 35	236 ± 27	242 ± 39
Days 6 - 18	195 ± 37	198 ± 34	196 ± 31	119 ± 64†
Days 18 - 29	165 ± 47	166 ± 41	178 ± 26	180 ± 37

*Mean ± S.D. for pregnant females.
†Significantly different from control by Newman-Keuls test, $p < 0.05$.

TABLE 3a

Maternal Clinical Signs* - Pretreatment (Days 0-5)

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Number of animals observed	13	15	15	18
Number with signs	8	7	5	9
Orange-rust urine		1		2
Diarrhea	8	5	4	6
Small amount of feces				1
Small black feces				1
Yellow-stained nose		1		1
Yellow stain on top of head			1	

*Pregnant females.

TABLE 3b

Maternal Clinical Signs* - Treatment (Days 6-18)

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Number of animals observed	13	15	15	18
Number with signs	10	11	14	18
Orange-rust colored urine	2	5	7	16
Thick/foamy urine		1	4	16
Granular/foamy urine				3
Clear yellow urine				1
Red urine				2
Red material in urine				2
Small amount of urine				1
No urine under cage				1
Diarrhea	8	6	8	7
Small amount of feces	1	1		9
Small feces	1			
Small black feces				1
No feces under cage				1
Mucus on feces				1
Bloody hair ball under cage				1
Red/yellow granular material under cage				1
Red material under cage				1
Yellow-stained nose	5	6	5	5
Stained perianal region		2		1
Brown material on leg/paws	1		1	2
Brown material on abdomen/tail				1
Yellow stain on top of head			1	
Red-stained nose or mouth			1	2
Orange-stained legs			1	1
Red-stained paws, hindquarters			1	2
Injured bloody toenails				3

*Pregnant females.

TABLE 3b (Concluded)

Maternal Clinical Signs* - Treatment (Days 6-18)

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Clear eye discharge		1		
Mucus or nasal discharge				2
Red nasal discharge				1
Blood in mouth at dosing	2	1	3	
Hair loss from underside	1		3	1
Short hair under chin			1	
Upper front teeth broken			1	
Strong rabbit/urine odor				1
Abscess appeared, drained, healed		1		
Deprived of water		2		
Ataxia				1
Inactive				2
Increased startle reflex				3
Convulsions				3
Twitching				1
Hypertonia				5
Hunched posture				4
Moved stiffly				2
Cyanosis				1
Tremors				1
Loss of consciousness				1
Prostrate				1
Rapid/shallow respiration				1
Dehydrated				1
Cried out after dosing				1
Cool to touch				1
Death or euthanized in moribund condition				6

*Pregnant females.

TABLE 3c

Maternal Clinical Signs* - Posttreatment (Days 19-29)

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Number of animals observed	13	15	15	12
Number with signs	4	8	6	12
Orange-rust colored urine			2	9
Thick/foamy urine			2	6
Red urine				1
Diarrhea	1			1
Small amount of feces	1	3	3	4
Small feces		1		
No feces under cage				1
No urine or feces under cage				2
Mucus on feces				1
Hair in feces			1	
Yellow-stained nose	2	3		1
Yellow-stained forepaws				1
Stained perianal region		1		
Brown material on abdomen/tail				1
Mucus or nasal discharge		1		2
Hair loss from underside	1			
Abscess healed		1		
Deprived of water			2	2
Inactive		1		
Pulling hair for nesting			1	
Red material under cage				2
Clump of mucus under cage				1
Convulsions				1
Hypertonia				1
Prostrate				1
Tremors				1
Increased salivation				1
Death or euthanized in moribund condition				1

*Pregnant females.

TABLE 4

Maternal Gross Necropsy Findings at Cesarean Section

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Number examined	13	15	15	11
Number with findings	10	11	12	9
Cysts on fallopian tubes	7	6	9	5
Dark red fallopian tubes	3	3	4	1
Red inflamed fallopian tubes			1	
Dark spots on ovary		2	2	
Cysts in adipose tissue				1
Fragile uterus	1			
Small pale liver	1			
Blotchy or mottled liver		1		1
Mass on liver	1			
Necrotic lung tissue				1
Cyst on lobe of lung				1
Mass on lung		1		
Red mass on pancreas	2	2		
Dark spots on pancreas			1	1
Dilated renal pelvis	1		1	1
Spots on kidney		2		
Cavitation of kidney medulla		1		1
Blotchy kidney			1	1
Pale kidney				1

TABLE 5

Effect of Nitroguanidine on Mean Gestational Data*

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Corpora lutea	10.3 ± 2.0	11.2 ± 2.5	11.1 ± 1.7	11.0 ± 1.9
Implantations	9.5 ± 1.5	10.2 ± 1.8	9.3 ± 2.0	9.6 ± 2.0
Implantation efficiency†	93.5 ± 9.9	92.9 ± 10.7	95.9 ± 18.3	90.1 ± 15.6
Resorption	0.2 ± 0.4	0.9 ± 0.5	0.5 ± 0.6	0.9 ± 1.4
Percent resorption§	2.2 ± 4.1	9.3 ± 5.0°	6.6 ± 8.3°	9.7 ± 15.1°
Number of fetuses	9.3 ± 1.3	9.0 ± 1.6	9.3 ± 3.0	8.7 ± 2.2
Live	100.0 ± 0.0	97.5 ± 5.3	99.3 ± 2.8	98.2 ± 3.8
Percent live«	0.0 ± 0.0	0.3 ± 0.6	0.1 ± 0.3	0.2 ± 0.4
Dead	0.0 ± 0.0	2.5 ± 5.3	0.7 ± 2.8	1.8 ± 3.8
Percent dead≈				

*Mean ± S.D./litter.
†[Implantations/corpora lutea] x 100
§[Resorptions/implantations] x 100
«[Live/(live + dead)] x 100
≈[Dead/(live + dead)] x 100
°Significantly different from control by the nonparametric multiple comparisons test, $p < 0.05$.

TABLE 6

Effect of Nitroguanidine on
Mean Litter Size, Sex, Weight, and Length*

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Number of fetuses	9.3 ± 1.3	9.0 ± 1.6	9.3 ± 3.0	8.7 ± 2.2
Number of males	4.0 ± 2.3	4.4 ± 2.0	4.3 ± 2.4	4.0 ± 1.2
Number of females	5.3 ± 2.1	4.6 ± 1.7	4.9 ± 2.0	4.7 ± 1.6
Percent males	42.4 ± 23.0	48.4 ± 20.2	44.1 ± 17.1	47.1 ± 13.6
Weight (g) males	42.8 ± 3.1	42.4 ± 5.3	43.6 ± 4.7	37.0 ± 7.0†
Weight (g) females	43.4 ± 3.8	40.8 ± 5.7	41.3 ± 5.5	36.2 ± 6.7†
Length (cm) males	10.5 ± 0.3	10.4 ± 0.4	10.6 ± 0.5	10.0 ± 0.7
Length (cm) females	10.5 ± 0.4	10.3 ± 0.5	10.4 ± 0.5	9.9 ± 0.6

*Mean ± S.D./litter
†Significantly different from control by Newman-Keuls test, $p < 0.05$.

TABLE 7

Effect of Nitroguanidine on
External Malformations and Variations*

	Nitroguanidine (mg/kg/day)			
Examination Finding	0	100	316	1000
Total number	121/13	135/15	131/15	87/10
Malformations				
Cleft palate				1/1
Ectrodactyly		1/1		
Variations				
Bloated abdomen				1/1

*Data presented as fetuses/litters.

TABLE 8

Effect of Nitroguanidine on
Visceral Malformations and Variations*

	Nitroguanidine (mg/kg/day)			
Examination Finding	0	100	316	1000
Total number	121/13	135/15	131/15	87/10
Malformations				
Cleft palate				1/1†
Ureter transversed midline				1/1†
Variations				
Enlarged heart ventricle				1/1
Dilated renal pelvis		1/1	1/1	
Elongated ovaries			1/1	

*Data presented as fetuses/litters.
†Both malformations occurred in the same fetus.

TABLE 9

Effect of Nitroguanidine on
Skeletal Malformations and Variations*

	Nitroguanidine (mg/kg/day)			
Examination Finding	0	100	316	1000
Total number	121/13	135/15	131/15	87/10
Malformations				
Ectrodactyly		1/1		
Cleft palate				1/1
Variations				
Sutural bone			1/1	1/1
Dot of ossification adjacent to 7th cervical vertebra	1/1	7/4		
21 vertebra (thoracic, lumbar, and sacral)		1/1		
Vertebral arch, centrum incomplete ossification				1/1
Ribs short, not parallel				1/1
Rib not ossified				1/1
Mid section of rib not ossified				1/1
Sternebrae				
4 ossified		2/2	1/1	1/1
5 ossified	15/8	21/8	29/9	16/6
Split	6/3	4/4	2/2	2/2
Partially ossified	10/5	24/8	20/10	15/8
Diagonally ossified	2/2	1/1	2/1	2/2
Scrambled	1/1			
Fused				1/1
Dumbbell shaped	2/2	1/1	1/1	1/1
Misshaped	2/2	1/1		1/1
Dot of ossification above first sternebrae	3/3	1/1		

*Data presented as fetuses/litters.
A single fetus may have more than one abnormality and, therefore, will be included more than once in this table.

TABLE 9 (Concluded)

Effect of Nitroguanidine on
Skeletal Malformations and Variations*

Examination Finding	Nitroguanidine (mg/kg/day) 0	100	316	1000
Variations (Continued)				
Olecranon not ossified	1/1	15/4	9/3	18/4
Patellae not ossified	6/3	14/7	10/5	14/5
Pubis not ossified				4/1
Number of phalanges ossified				
Forepaw				
14	7/3	17/8	11/5	11/6
13	1/1	1/1	4/3	4/1
12		1/1		1/1
11		1/1		1/1
Hindpaw				
11		2/2	1/1	4/2

*Data presented as fetuses/litters.
A single fetus may have more than one abnormality and, therefore, will be included more than once in this table.

TABLE 10

Effect of Nitroguanidine on the Incidence of Fetal Malformations and Variations*

	Nitroguanidine (mg/kg/day)			
	0	100	316	1000
Total number	121/13	135/15	131/15	87/10
Any (External/Visceral/Skeletal)				
Malformations		1/1		1/1
Variations	46/12	65/13	62/14	52†/10
External examination				
Malformations		1/1		1/1
Variations				1/1
Visceral examination				
Malformations				1/1
Variations		1/1	2/2	1/1
Skeletal examination				
Malformations		1/1		1/1
Variations	46/12	64/13	61/14	52†/10

*Data presented as fetuses/litters.
†Significantly different from control by Marascuilo's method of multiple comparison of proportions, $p < 0.05$.

DISCUSSION

The health effects of nitroguanidine are being determined because of the Army's decision to incorporate nitroguanidine in its triple-base propellants. Previously, this laboratory showed that nitroguanidine was slightly toxic in rats and mice following acute oral administration, was nonirritating to the skin and eyes of rabbits, and was nonreactive in a dermal sensitization study in guinea pigs (14). A subchronic toxicity study in rats with doses as high as a "limit dose" of 1000 mg/kg/day mixed in the diet for 14 days produced no definitive toxicological effects (15). This lack of toxicity was supported by metabolic fate studies that indicated that nitroguanidine was absorbed 100% following oral administration and was excreted unchanged in the urine, 60-80% within the first 8 hours (16). In a developmental toxicity study in rats, nitroguanidine given by oral gavage on gestational days 6 through 15 at 1000 mg/kg/day produced decreased food consumption, maternal weight loss, and smaller fetuses with an increased incidence of retarded ossification of the sternebrae, caudal vertebrae, and pubis. The developmental toxicity no-observed-effect level for nitroguanidine in rats was 316 mg/kg/day (17).

The predominant sign of maternal toxicity observed in this study was death in ten animals (six animals died and four moribund animals were terminated) in the 1000-mg/kg/day group. It is doubtful that these deaths were attributable to a direct pharmacological effect. Necropsy findings on the ten animals were varied with no finding common to all. The general failure to thrive of these animals suggested that the high concentrations of nitroguanidine necessary to administer the 1000-mg/kg/day dose by oral intubation interfered with the digestive processes of the animals in this group. This is supported by the decreased food consumption and weight loss during the treatment period. Additionally, one animal had a ruptured stomach, another animal with two masses of dosing material in the stomach had a ruptured esophagus. The tubing used to administer the test compound was smooth and flexible, not likely to tear healthy tissue. Nitroguanidine also reduced food consumption and decreased body weight in rats when given by oral gavage at 1000 mg/kg/day (17). Necropsy findings on several rabbits with convulsions suggested that *Encephalitozoon cuniculi* was a possible etiology. Stress was indicated as a contributing factor in the death of the animal with severe lymphoid depletion. Possible hemoglobinuria could have occurred as a result of the test compound in the animal with nephrosis. The only dose-related adverse maternal effects which occurred in the 100- or 316-mg/kg/day groups were a low frequency incidence of orange-rust colored urine and thick and foamy urine.

The four primary manifestations of developmental toxicity are death of the conceptus, malformation, retarded

development, and functional deficit. This study was designed to screen for the first three. In a developmental toxicity test the fetal examination findings may range in severity from slightly retarded development or minor variations to major malformations. Retarded development may be transitory, for example, caused by decreased maternal food consumption, and the retarded offspring may catch up quickly after birth or after weaning. Minor variations from normal may not have an adverse effect on the function and quality of life of the offspring. Major structural malformations, such as malformed or missing organs or limbs, can either be life threatening or severely limit the functioning and longevity of the offspring. A test substance is considered developmentally toxic if, when administered at a dose level that is not overtly maternally toxic, it produces malformations at a significantly higher incidence than in the controls. Although variations are not as serious as malformations, a significantly increased incidence of variations, in comparison to the controls, is a sign of some fetal or maternal toxicity (18). Spontaneous malformations are those that occur randomly, usually at low frequency, and are of unknown cause, and whose incidence is not dose-related.

Nitroguanidine increased the number of litters with resorptions in the 100-mg/kg/day and 1000-mg/kg/day groups and the percent resorption per litter in all dose groups in comparison to the control group. One dam in the 1000-mg/kg/day group had 100% of implants resorbed. An increased incidence of resorptions is a manifestation of developmental toxicity.

In this study each fetus was examined externally at cesarean section and then for visceral and skeletal abnormalities. The findings on each fetus were described and categorized as either variations or malformations, depending on the severity or whether the changes were permanent. The finding of 13 ribs (unilateral, bilateral, or rudimentary) was not included in this report because it occurred at a high frequency and was not dose-related. Those findings categorized as variations included such transitory findings as retarded ossification (includes those fetuses with fewer than six sternebrae, fewer than 15 phalanges per forepaw, and fewer than 12 phalanges per hindpaw ossified) and minor deviations from normal that may or may not be permanent such as slightly misshapen sternebrae or ribs, extra dots of ossification, dilated renal pelvis, elongated ovaries, enlarged heart ventricle, and bloated abdomen. Findings of more serious consequence that were categorized as malformations were cleft palate, displaced ureter, and ectrodactyly.

The retarded development in the 1000-mg/kg/day group resulted in fetuses that were significantly lighter in weight and had an increased incidence of skeletal variations in

comparison to the controls. This retarded development could be attributed to maternal toxicity rather than to a direct effect of nitroguanidine on the fetus. The 1000-mg/kg/day group dams lost weight and consumed less food than the controls during the treatment period.

The malformations observed in this study are considered spontaneous because they are not dose-related and occurred at a low frequency. One dam in the 1000-mg/kg/day group had nasal discharge from Days 7 through 29, and marked necrosis of the lung was observed at cesarean section. The fetus with multiple malformations (cleft palate and displaced ureter), the fetus with bloated abdomen at external examination, and the fetus with enlarged heart ventricle at visceral examination were in her litter. The malformations and variations which occurred in this litter could be attributed to the compromised condition of the dam. Two fetuses (one in the 100-mg/kg/day group and one in the 1000-mg/kg/day group) out of a total of 474 fetuses in the study were malformed. The incidence of spontaneous malformations in this study is similar to that published by Palmer (3) and historical controls from this laboratory (2) and is not attributed to nitroguanidine.

CONCLUSION

There was no evidence of nitroguanidine producing teratogenicity (malformations) in rabbits under conditions of this study. Nitroguanidine, administered at a dose level that does not produce overt maternal toxicity, has the potential to cause developmental toxicity (increased resorptions).

REFERENCES

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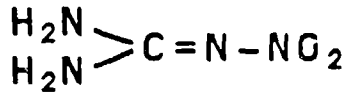
Appendix A: CHEMICAL DATA

Chemical name: Nitroguanidine (NGu)

Other listed names: Guanidine, Nitro; alpha-Nitroguanidine; beta-Nitroguanidine

LAIR Code: Phase I: TP036A
Phase II: TP036B

Structural formula:



Molecular formula: $CH_4N_4O_2$

Molecular weight: 104.1

pH range of dosing suspensions: 6.7 - 7.4[1]

Physical state: White Powder

Melting point: 232° C[2]

Source: Hercules Aerospace Division
Sunflower Ammunition Plant
DeSoto, Kansas

Lot No. Phase I: SOW84K010-A-001
Phase II: SOW85F011-028

Appendix A (Cont.): CHEMICAL DATA

Analytical data/purity: The major peaks in the infrared spectrum of the compound were observed at 3450, 3396, 3342, 3278, 3201, 1666, 1634, 1525, 1404, 1314, 1151, 1045, 782 cm^{-1}.(3) The spectrum obtained for the test compound in our lab was identical to the spectrum for TP36B (4) and to the Sadtler standard spectrum for nitroguanidine(5). HPLC showed only one peak (retention time 4.9 min for TP36A (6); 4.8 min for TP36B) (7). The conditions employed were as follows: column, Brownlee RP-18 (4.6 x 250 mm); solvent, 10% methanol-90% water; flow rate, 0.7 ml/min; oven temperature, 50°C; monitoring wavelength, 265 nm.

Stability: Stable in 1% carboxymethylcellulose for at least four months (see Appendix C)

References:

1. Wheeler CR. Nitrocellulose-Nitroguanidine Projects Laboratory Notebook #85-12-022, p. 26. Letterman Army Institute of Research, Presidio of San Francisco, CA.

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7. *Ibid.*, pp.33-5.

Appendix A (Cont.): CHEMICAL DATA

DESCRIPTION SHEET FOR EXPLOSIVES, CHEMICALS, ETC
(DRSAR-P-702-109)

ROR CONTROL SYMBOL: EXEMPT-Para 7-2a AR 335-15 | PAGE: 1 OF 1

TO: Commander, US Army Armament Munitions and Chemical Command, Attn: DRSMC-QAB, Rock Island, ILL. 61299

FROM: Sunflower Army Ammunition Plant, DeSoto, Kansas 66018

DATE: October 9, 1984

MATERIAL: Nitroguanidine

MANUFACTURER: Hercules Aerospace Division, Hercules Inc.

CONTRACT NO.: DAAA-09-77-C-4016 CLIN 0295

SECTION A - DESCRIPTION OF LOTS

FROM NUMBER	THRU NUMBER	TOTAL NO. LOTS	TOTAL NET AMOUNT ACCEPTED
SOW84K010A001	-	1	25 pounds

PLACE MANUFACTURED: Sunflower Army Ammunition Plant

SPECIFICATION AND AMENDMENT/DRAWING NO.: MIL-N-00494B dtd. 17 July 1984

SECTION B - DESCRIPTION OF MATERIAL

Property	Requirement Min.	Requirement Max.	Analysis *
Purity, %	99.0		99.20
Ash Content, %		0.30	0.12
pH Value	4.5	7.0	6.0
Acidity (as H_2SO_4), %		0.06	0.0
Total Volatiles, %		0.25	0.16
Sulfates (as H_2SO_4), %		0.20	0.17
Impurities, H_2O Insoluble, %		0.20	0.02
Particle Size, microns	3.4	6.0	3.5
Color			White
Consistency			Crystalline, Free Flowing

* Combined averages of sampling taken in accordance with MIL-N-00494B, Para. 4.4.3.2.

REMARKS

1) Packaging: Level C Fiber drums per specification DOT 21C60
2) This lot was manufactured 5 October 1984 and is submitted as First Article in compliance with Paragraph 4.3 of MIL-N-00494B.
3) Guanidine Nitrate supplied by SKW-American Hoesch was used in manufacture of this lot.

SECTION C - CERTIFICATION

SAMPLING CONDUCTED BY: Hercules Aerospace Division

TESTING CONDUCTED BY: rcules Aerospace Division

THE ABOVE MATERIAL COMPLIES WITH ALL SPECIFICATION REQUIREMENTS AND IS CERTIFIED TRUE AND CORRECT.

9 Oct 84 (DATE) — A. W. English (SIGNATURE)

THE ABOVE DESCRIBED LOTS ARE HEREBY ACCEPTED

FOR THE COMMANDER

10 OCT 1984 (DATE) — CHIEF, QA DIV, SFAP (TITLE) — (SIGNATURE)

ARACOM Form 213-R, 18 AUG 77 — REPLACES ARACOM FORM 213-R, 15 JUL 75 (ITEM 7), WHICH IS OBSOLETE.

Appendix A (Cont.): CHEMICAL DATA

DESCRIPTION SHEET FOR EXPLOSIVES, CHEMICALS, ETC

DRSAR-P-202-(109)

EXEMPT. Para 7-2a AR 335-15 | Page 2 of 2

TO: Commander, US Army Armament Munitions and Chemical Command, Attn: DRSMC-QAD, Rock Island, ILL. 61299

FROM: Sunflower Army Ammunition Plant, DeSoto, Kansas 66018

DATE: June 26, 1985

MATERIAL: Nitroguanidine

MANUFACTURER: Hercules Aerospace Company

CONTRACT NO.: DAAA09-76-C-4016

SECTION A - DESCRIPTION OF LOTS

FROM NUMBER	THRU NUMBER	TOTAL NO. LOTS	TOTAL NET AMOUNT ACCEPTED
SOW85F011-028	--	1	10,950 pounds

PLACE MANUFACTURED: Sunflower Army Ammunition Plant

SPECIFICATION AND AMENDMENT/ORDERING NO.: MIL-N-00494B dtd. 17 July 1984

SECTION B - DESCRIPTION OF MATERIAL

TEST REQUIREMENT--SHIFT AVERAGE

			MAX→	- -	0.30%	7.0	0.06%	0.20%	0.20%	0.20%	6.0
			MIN→	99.00%	- -	4.5	- -	- -	- -	- -	3.4
LOT NO.	DATE	SHIFT	DRUMS	PURITY	ASH	pH	ACIDITY	H₂O	SULFATES	W.I.	FSSS
SOW85F011-028			415-534								
-028			537-548								
-028	6-20-85	8-4	557-566	*	*	*	*	*	*	*	*
-028			568-572								
-028			574-576								
TOTAL DRUMS			219								

*Testing for requirement at reduced frequency per MIL-STD-1235A.
Sampling and testing in accordance with MIL-N-00494B and MIL-STD-1235A. The test result reported is an average of shift samples on the date the lot was packed.

REMARKS
1) Packaging: Level C - Fiber drums per specification DOT21C60.
2) Interfix number 011 identifies lots manufactured with Sunflower produced guanidine nitrate.
3) The average bulk density for Lot SOW85F011-028 is 0.262 gm/cc as determined by Method 201.3 of MIL-STD-650.

SECTION C - CERTIFICATION

SAMPLING CONDUCTED BY: Hercules Aerospace Company

TESTING CONDUCTED BY: Hercules Aerospace Company

THE ABOVE MATERIAL COMPLIES WITH ALL SPECIFICATION REQUIREMENTS AND IS CERTIFIED TRUE AND CORRECT

22 June 1985 (DATE) A. W. English, Quality Assurance Dept. (TITLE)

THE ABOVE DESCRIBED LOTS ARE HEREBY ACCEPTED

FOR THE COMMANDER

25 JUNE 1985 (DATE) Chief, QA Division (TITLE)

Appendix B: ANIMAL DATA

Species: Rabbit

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry
Watsonville, CA

Sex: 78 Females and 18 Males

Age:

Males: Proven breeders, approximately 5 1/2 months old at arrival at LAIR.

Females: Nulliparous, approximately 4 months at arrival at LAIR, approximately 5 months at start of breeding.

Animal identification numbers:

Males: 86F241 - 86F258

Females: Phase I: 86F201 - 86F240
Phase II: 86F283 - 86F322

	Phase I	Phase II
Weight range (kg) at start of breeding:		
Males	3.8 - 4.7	4.2 - 4.7
Females	3.1 - 4.3	3.1 - 4.3

Appendix C: CHEMICAL ANALYSIS

HOMOGENEITY*

A suspension of nitroguanidine (200 mg/ml, 300 ml) was prepared in 1% carboxymethylcellulose. This suspension was subsequently used to prepare two more dilute suspensions of approximately 60 mg/ml (20 ml) and 20 mg/ml (20 ml) in 20-ml vials. The suspensions were stirred well, and aliquots of 1 ml were removed from the top, middle, and bottom layers of each suspension. The aliquots were transferred to either 500- or 1000-ml volumetric flasks and diluted to volume with water. After one more dilution (see table below) the optical absorbance at 264 nm was determined.

The concentration of the original suspension was then calculated using the dilution and absorbance data. A comparison of the individual values to the mean value of the appropriate group showed no deviation larger than 3%.

Target Concentration mg/ml	Area Sample	1st Dilution ml	2nd Dilution ml	Absorbance at 264 nm	Concentration mg/ml
20	top	500	5	1.305	23.4
	middle			1.304	23.4
	bottom			1.302	23.4
60	top	1000	10	1.021	73.4
	middle			1.043	75.0
	bottom			1.076	77.3
200	top	1000	25	1.150	206.6
	middle			1.163	209.0
	bottom			1.135	203.9

*Wheeler CR. Nitrocellulose-Nitroguanidine Projects. Laboratory Notebook #85-12-022, p. 27-29. Letterman Army Institute of Research. Presidio of San Francisco, CA.

Appendix C (Cont.): CHEMICAL ANALYSIS*

All dosing suspensions were analyzed by transferring 1-ml aliquots of suspension to a volumetric flask and diluting to volume. An aliquot of the first dilution was subsequently transferred to a second volumetric flask and diluted to volume (for total dilution see dilution factor in table below). The absorbance spectrum (200-340 nm) of the final dilution was determined with a UV/VIS spectrophotometer. The absorbance at 260 nm was then used to calculate the concentration of nitroguanidine according to the following equation which is based on Beer's law:

$$\text{Concentration (Conc.)} = \frac{\text{Absorbance} \times \text{dilution factor} \times \text{nitroguanidine molecular weight (104 g/mole)}}{\text{molar extinction coefficient (14,470)}}$$

Date Prepared	Date Analyzed	Target Conc. mg/ml	Dilution Factor	Absorbance nm	Conc. Determined by Analysis mg/ml	% Target Conc.
10 Oct 86	22 Jan 87	20.0	2,500	1.379	19.8	99 0
10 Oct 86	22 Jan 87	63.2	10,000	0.888	63.8	100.9
10 Oct 86	22 Jan 87	200.0	20,000	1.118	200.9	100.4
14 Jan 87	16 Jan 87	20.0	2,500	1.089	19.6	98.0
14 Jan 87	16 Jan 87	63.2	10,000	0.893	64.2	101.6
14 Jan 87	16 Jan 87	200.0	20,000	1.114	200.2	100.1

All concentrations of nitroguanidine were within 2% of the target concentration. In each case, the pattern of the spectrum obtained on scanning from 200 to 340 corresponded exactly to that expected for nitroguanidine. Suspensions of nitroguanidine in 1% carboxymethylcellulose have been shown to be stable for at least four months.†

*Wheeler CR. Toxicity Testing of Propellants. Laboratory Notebook #85-12-022, pp. 30-32. Letterman Army Institute of Research, Presidio of San Francisco, CA.

†*Ibid.*, pp.31-2.

Appendix D: SCHEDULE OF STUDY EVENTS

DATE	EVENT
23 Jul 86	Date protocol approved.
25 Sep 86	Male and female rabbits for Phase I arrived at LAIR.
14 - 28 Oct 86	Phase I breeding.
20 Oct - 15 Nov 86	Phase I females dosed.
12 - 26 Nov 86	Cesarean sections, Phase I females.
18 Dec 86	Female rabbits for Phase II arrived at LAIR.
12 - 21 Jan 87	Phase II breeding.
18 Jan - 8 Feb 87	Phase II females dosed.
10 - 19 Feb 87	Cesarean sections, Phase II females.

Appendix E: INDIVIDUAL MATERNAL BODY WEIGHTS*

Control Animals

Maternal ID	Day of Gestation							Weight Change	
						Gravid	Correct		
	0	6	12	18	23	29	29	29C-0†	18-6§
86F212	3.25	3.64	3.94	4.18	4.47	4.59	4.14	.89	.54
86F214	3.85	4.02	3.98	3.89	4.08	4.29	3.78	-.07	-.13
86F218	3.65	3.87	4.24	4.33	4.36	4.48	3.85	.20	.46
86F231	3.99	4.25	4.36	4.49	4.69	4.80	4.23	.24	.24
86F235	3.61	4.01	4.32	4.46	4.58	4.6	4.06	.45	.45
86F236	3.96	3.76	4.25	4.43	4.67	4.83	4.33	.37	.67
86F237	3.93	3.94	3.89	3.89	3.97	3.61	3.25	-.68	-.05
86F297	3.42	3.62	3.65	3.74	3.86	3.92	3.38	-.04	.12
86F303	3.82	4.19	4.31	4.47	4.62	4.74	4.33	.51	.28
86F304	4.05	4.31	4.39	4.46	4.62	4.65	4.11	.06	.15
86F309	4.26	4.51	4.60	4.75	4.92	5.09	4.55	.29	.24
86F316	3.71	4.00	4.09	4.13	4.07	4.26	3.72	.01	.13
86F321	3.88	4.36	4.45	4.58	4.59	4.80	4.32	.44	.22

*Weights in kg.
†Study period (Day 29 Corrected - Day 0).
§Treatment period (Day 18 - Day 6).

Appendix E (Cont.): INDIVIDUAL MATERNAL BODY WEIGHTS*

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Day of Gestation							Weight Change	
						Gravid	Correct		
	0	6	12	18	23	29	29	29C-0†	18-6§
86F202	3.82	4.21	4.30	4.35	4.42	4.53	4.11	.29	.14
86F203	4.17	4.81	5.01	5.12	5.22	5.54	4.99	.82	.31
86F210	3.77	4.06	4.21	4.36	4.52	4.59	4.06	.29	.30
86F225	3.13	3.46	3.43	3.63	3.71	3.93	3.40	.27	.17
86F226	3.76	3.71	4.03	4.18	4.33	4.44	4.07	.31	.47
86F230	3.22	3.49	3.55	3.71	3.80	3.92	3.58	.36	.22
86F232	4.04	4.28	4.53	4.64	4.70	4.72	4.22	.18	.36
86F239	3.56	3.92	4.11	4.25	4.43	4.55	4.07	.51	.33
86F292	4.16	4.50	4.59	4.68	4.94	5.08	4.50	.34	.18
86F295	3.84	4.08	4.12	4.17	4.38	4.46	4.01	.17	.09
86F300	4.01	4.36	4.41	4.42	4.55	4.75	4.26	.25	.06
86F308	3.35	3.48	3.41	3.62	3.53	3.42	3.03	-.32	.14
86F310	3.73	3.92	3.63	4.21	4.30	4.43	3.98	.25	.29
86F311	3.77	4.17	4.23	4.39	4.50	4.57	4.09	.32	.22
86F320	3.78	4.04	4.10	4.20	4.32	4.55	3.97	.19	.16

*Weights in kg.
†Study period (Day 29 Corrected - Day 0).
§Treatment period (Day 18 - Day 6).

Appendix E (Cont.): INDIVIDUAL MATERNAL BODY WEIGHTS*

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Day of Gestation							Weight Change	
						Gravid	Correct		
	0	6	12	18	23	29	29	29C-0†	18-6§
86F215	3.87	4.06	4.17	4.22	4.44	4.58	4.12	.25	.16
86F217	4.04	4.42	4.63	4.58	4.72	4.91	4.18	.14	.16
86F220	3.75	4.04	4.21	4.30	4.04	4.49	3.97	.22	.26
86F223	3.17	3.60	3.67	3.86	3.91	4.01	3.52	.35	.26
86F224	4.02	4.30	4.33	4.45	4.64	4.80	4.35	.33	.15
86F227	3.63	4.04	4.12	4.26	4.36	4.48	3.97	.34	.22
86F234	3.72	4.14	4.44	4.56	4.77	4.94	4.45	.73	.42
86F238	3.61	3.86	3.80	4.02	4.14	4.35	3.87	.26	.16
86F284	4.27	4.59	4.63	4.83	4.96	5.07	4.47	.20	.24
86F285	3.46	3.75	3.84	3.91	4.04	4.23	3.86	.40	.16
86F298	3.75	3.94	3.97	4.08	4.22	4.35	3.88	.13	.14
86F301	3.96	4.28	4.25	4.39	4.66	4.66	4.18	.22	.11
86F313	3.87	4.07	4.06	4.02	4.22	4.32	3.94	.07	-.05
86F314	3.84	4.13	4.15	4.14	4.30	4.36	4.22	.38	.01
86F322	3.41	3.52	3.60	3.74	3.82	3.97	3.54	.13	.22

*Weights in kg.
†Study period (Day 29 Corrected - Day 0).
§Treatment period (Day 18 - Day 6).

Appendix E (Cont.): INDIVIDUAL MATERNAL BODY WEIGHTS*

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Day of Gestation							Weight Change	
	0	6	12	18	23	Gravid 29	Correct 29	29C-0†	18-6§
86F209	3.29	3.82	2.85	«					
86F216	3.60	4.07	3.40	«					
86F221	≈	4.24	4.36	4.58	4.83	4.87	4.35	≈	.34
86F228	3.46	4.05	4.21	4.22	4.39	4.38	3.96	.50	.17
86F229	3.58	3.91	«						
86F233	3.77	4.13	4.15	3.77	«			«	-.36
86F240	3.68	4.18	4.21	4.26	4.47	4.58	4.11	.43	.08
86F283	3.46	4.11	4.11	4.22	4.40	4.58	4.12	.66	.11
86F288	4.11	4.38	4.28	4.18	4.57	4.74	4.26	.15	-.20
86F290	3.69	4.02	3.86	3.37	3.28	3.58	3.58	-.11	-.65
86F293	3.54	3.82	3.71	«					
86F294	3.62	3.81	3.77	3.75	4.12	4.27	3.98	.36	-.06
86F296	3.85	4.15	4.16	4.26	4.39	4.54	4.00	.15	.11
86F302	3.74	3.87	3.83	3.50	3.60	4.03	3.80	.06	-.37
86F312	3.89	4.36	4.32	4.09	4.43	4.72	4.27	.38	-.27
86F315	3.55	3.68	«						
86F317	3.71	3.73	3.66	3.59	3.83	3.89	3.67	-.04	-.14
86F319	3.66	3.93	3.48	«					

*Weights in kg.
†Study period (Day 29 Corrected - Day 0).
§Treatment period (Day 18 - Day 6).
«Animal died.
≈Missing data.

Appendix F

INDIVIDUAL MATERNAL FOOD CONSUMPTION*

Control Animals

Maternal ID	Days of Gestation 1-6	6-18	18-29
86F212	254†	237	242
86F214	229	133	204
86F218	248	164	141
86F231	233	201	152
86F235	204	239	163
86F236	215	227	225
86F237	243†	145	78
86F297	209	172	152
86F303	255	231	206
86F304	213	170	133
86F309	269	222	193
86F316	242	177	103
86F321	247	222	156

*Average daily consumption in g.
†Reflects 4 days of data.

Appendix F (Cont.)

INDIVIDUAL MATERNAL FOOD CONSUMPTION*

100 mg/kg/day
Nitroguanidine Animals

Maternal ID	Days of Gestation 1-6	6-18	18-29
86F202	244	206	142
86F203	267	202	253
86F210	237	195	160
86F225	234	169	134
86F226	201	174	190
86F230	234	210	180
86F232	298†	246	143
86F239	279†	230	197
86F292	285	237	196
86F295	214	191	172
86F300	247	200	152
86F308	176	117	66
86F310	190	162	167
86F311	265	237	198
86F320	232	194	146

*Average daily consumption in g.
†Reflects 4 days of data.

Appendix F (Cont.)

INDIVIDUAL MATERNAL FOOD CONSUMPTION*

316 mg/kg/day
Nitroguanidine Animals

Maternal ID	Days of Gestation		
	1-6	6-18	18-29
86F215	242	196	194
86F217	238	184	210
86F220	236	211	163
86F223	220	188	134
86F224	237	219	189
86F227	231	208	166
86F234	261	262	219
86F238	226	171	180
86F284	271	238	180
86F285	206	178	177
86F298	214	173	157
86F301	273	190	187
86F313	190	132	131
86F314	286	212	218
86F322	216	171	169

*Average daily consumption in g.

Appendix F (Cont.)

INDIVIDUAL MATERNAL FOOD CONSUMPTION*

1000 mg/kg/day
Nitroguanidine Animals

Maternal ID	Days of Gestation 1-6	6-18	18-29
86F209	245	71≈	§
86F216	276	94≈	§
86F221	«	221	184
86F228	299	226	189
86F229	257	105**	§
86F233	247	163	§
86F240	242	197	182
86F283	254	168	206
86F288	285	118	216
86F290	220	63	121
86F293	214†	73††	§
86F294	250	138	228
86F296	267	169	145
86F302	207	110	146
86F312	298	131	224
86F315	185	7**	§
86F317	160	65	143
86F319	206	16§§	§

*Average daily consumption in g.
†Reflects 4 days of data.
§Animal died.
«Missing data.
≈Reflects 7 days of data.
**Reflects 5 days of data.
††Reflects 10 days of data.
§§Reflects 9 days of data.

Appendix G: INDIVIDUAL MATERNAL CLINICAL SIGNS

Control Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F212	4	23 Oct 86	Diarrhea
	6	25 Oct 86	Orange-rust colored urine
	7	26 Oct 86	Yellow-stained nose
	10	29 Oct 86	Diarrhea
	10-20	29 Oct-8 Nov 86	Yellow-stained nose
	15	3 Nov 86	Diarrhea
86F214	6	20 Oct 86	Diarrhea
	10	24 Oct 86	Orange-rust colored urine
	13-14	27-28 Oct 86	Blood in mouth at dosing
	16-17	30-31 Oct 86	Small feces
86F218	7	26 Oct 86	Yellow-stained nose
	8	27 Oct 86	Diarrhea
86F231	0-29	20 Oct-29 Nov 87	Normal
86F235	5	26 Oct 86	Diarrhea
86F236	2	23 Oct 86	Diarrhea
	4-5	25-26 Oct 86	Diarrhea
	6	27 Oct 86	Blood in mouth at dosing
	8	29 Oct 86	Diarrhea
	10-15	31 Oct-5 Nov 86	Diarrhea
	12-14	2-4 Nov 86	Brown material on legs
	16	6 Nov 86	Yellow-stained nose
	17-19	7-9 Nov 86	Diarrhea
	18	8 Nov 86	Yellow-stained nose
	23-24	13-14 Nov 86	Diarrhea
	28	18 Nov 86	Diarrhea
86F237	9	31 Oct 86	Hair loss on inside thighs
	12	3 Nov 86	Hair loss on inside thighs
	15	6 Nov 86	Hair loss on inside thighs
	16-26	7-17 Nov 86	Hair loss on inside thighs and arm pits
	27-29	18-20 Nov 86	Small amount of feces
	29	20 Nov 86	Hair loss on underside

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

Control Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F297	2-4	17-19 Jan 87	Diarrhea
	7-8	22-23 Jan 87	Diarrhea
86F303	3	17 Jan 87	Diarrhea
86F304	3	17 Jan 87	Diarrhea
	9-10	23-24 Jan 87	Diarrhea
86F309	2-3	17-18 Jan 87	Diarrhea
	8	23 Jan 87	Diarrhea
86F316	3	23 Jan 87	Diarrhea
	8-11	28-31 Jan 87	Yellow-stained nose
	13	2 Feb 87	Yellow-stained nose
	16	5 Feb 87	Small amount of feces
86F321	13	2 Feb 87	Diarrhea
	13-14	2-3 Feb 87	Yellow-stained nose
	24	13 Feb 87	Yellow-stained nose
	28	17 Feb 87	Yellow-stained nose

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F202	9-11	24-26 Oct 86	Orange-rust colored urine
	11	26 Oct 86	Yellow-stained nose
	25	9 Nov 86	Small amount of feces
86F203	7	23 Oct 86	Blood in mouth at dosing
	10	26 Oct 86	Orange-rust colored urine
	10-11	26-27 Oct 86	Yellow-stained nose
	13-19	29 Oct-4 Nov 86	Stained perianal
	14	30 Oct 86	Diarrhea
86F210	4	20 Oct 86	Diarrhea
	7	23 Oct 86	Diarrhea Yellow-stained nose
	9	25 Oct 86	Orange-rust colored urine
	10	26 Oct 86	Yellow-stained nose
	13-20	30 Oct-5 Nov 86	Yellow-stained nose
86F225	0-29	21 Oct-19 Nov 86	Normal
86F226	4	20 Oct 86	Diarrhea
	6	22 Oct 86	Diarrhea
	6-7	22-23 Oct 86	Stained perianal
	8	24 Oct 86	Orange-rust colored urine
	10	26 Oct 86	Orange-rust colored urine
86F230	5	25 Oct 86	Orange-rust colored urine
	8-15	28 Oct-4 Nov 86	Hard round 1 cm diameter mass under chin
	16	5 Nov 86	Mass broke open exposing thick cream-colored pus; abscess drained
	17	6 Nov 86	Abscess drained
	18-19	7-8 Nov 86	Abscess healing
86F232	3-4	25-26 Oct 86	Diarrhea
	10-11	1-2 Nov 86	Diarrhea
	12	3 Nov 86	Yellow-stained nose
	28	19 Nov 86	Small amount of feces

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F239	10-11	1-2 Nov 86	Thick, foamy urine
	10-12	1-3 Nov 86	Diarrhea
	15	6 Nov 86	Orange-rust colored urine
86F292	5	17 Jan 87	Diarrhea
86F295	0-29	13 Jan-11 Feb 87	Normal
86F300	3	17 Jan 87	Diarrhea
	7	21 Jan 87	Yellow-stained nose
	7-8	21-22 Jan 87	Diarrhea
	9	23 Jan 87	Clear discharge from eye
	12	26 Jan 87	Clear discharge from eye
	14-19	28 Jan-2 Feb 87	Yellow-stained nose
86F308	14	29 Jan 87	Small amount of feces Deprived of water
	24-25	8-9 Feb 87	Small feces
	24-26	8-10 Feb 87	Small amount of feces
	25-28	9-12 Feb 87	Inactive
	27-28	11-12 Feb 87	Nasal discharge
86F310	3	18 Jan 87	Yellow-stained nose
	13	28 Jan 87	Deprived of water
86F311	6	25 Jan 87	Yellow-stained nose
	8-25	27 Jan-13 Feb 87	Yellow-stained nose
86F320	0-29	29 Jan-18 Feb 87	Normal

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F215	9	23 Oct 86	Blood in mouth at dosing
	11-12	25-26 Oct 86	Orange-rust colored urine
86F217	12	26 Oct 86	Yellow-stained nose
86F220	9	24 Oct 86	Orange-rust colored urine
	10	25 Oct 86	Diarrhea
	11	26 Oct 86	Yellow-stained nose
	11-12	26-27 Oct 86	Orange-rust colored urine
86F223	4	20 Oct 86	Diarrhea
	7	23 Oct 86	Diarrhea
	10-11	26-27 Oct 86	Orange-rust colored urine
	24	9 Nov 86	Pulling hair for nesting
86F224	6	29 Oct 86	Diarrhea
	6-12	29 Oct-4 Nov 86	Hair loss inside theighs
	8	31 Oct 86	Thick/foamy urine
	10	2 Nov 86	Thick/foamy urine
	19	11 Nov 86	Thick/foamy urine
	27	19 Nov 86	Small amount of feces Deprived of water
86F227	4	23 Oct 86	Yellow-stained top of head
	6-17	25 Oct-5 Nov 86	Yellow-stained top of head
	17	5 Nov 86	Diarrhea
	18	6 Nov 86	Yellow-stained nose
86F234	6-14	1-9 Nov 86	Short hair under chin
	7-14	2-9 Nov 86	Hair loss from thigh and between front legs
86F238	8-11	31 Oct-3 Nov 86	Diarrhea
	19	11 Nov 86	Thick/foamy urine
	27	19 Nov 86	Small amount of feces Deprived of water

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F284	7	19 Jan 87	Thick/foamy urine
	9-11	21-23 Jan 87	Orange-rust colored urine
	10	22 Jan 87	Blood in mouth at dosing Red-stained nose and paws
	11	23 Jan 87	Diarrhea
	13-16	25-28 Jan 87	Orange-rust colored urine
	21	2 Feb 87	Orange-rust colored urine
86F285	9	23 Jan 87	Orange-rust colored urine Thick/foamy urine
	12	26 Jan 87	Orange-rust colored urine
86F298	4	17 Jan 87	Diarrhea
	7	20 Jan 87	Upper front teeth broken
	10-11	23-24 Jan 87	Orange-rust colored urine
	13	26 Jan 87	Thick/foamy urine
	13-16	26-29 Jan 87	Orange-rust colored urine
	16	29 Jan 87	Diarrhea
	18-19	31 Jan-1 Feb 87	Orange-rust colored urine
	18-20	31 Jan-2 Feb 87	Hair in feces
86F301	2-3	17-18 Jan 87	Diarrhea
86F313	6-9	25-28 Jan 87	Brown material on forepaw
	12	31 Jan 87	Brown material on forepaw
	13	1 Feb 87	Diarrhea
	14	2 Feb 87	Brown material on forepaw
	15	3 Feb 87	Brown material on hindlegs
	18	6 Feb 87	Brown material on hindlegs
	25	13 Feb 87	Small amount of feces
86F314	4	23 Jan 87	Diarrhea
	8	27 Jan 87	Hair loss from inside leg
	11	30 Jan 87	Hair loss from inside leg
	13-14	1-2 Feb 87	Hair loss from inside leg
	15	3 Feb 87	Orange stained fore leg
86F322	11	31 Jan 87	Orange-rust colored urine
	14	3 Feb 87	Yellow-stained nose
	17	6 Feb 87	Blood in mouth at dosing

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F209	1	16 Oct 86	Diarrhea
	7	22 Oct 86	Granular/foamy urine
	9-10	24-25 Oct 86	Granular/foamy urine
	10	25 Oct 86	Red-stained hindquarters
	10-11	25-26 Oct 86	Red urine
	11	26 Oct 86	Yellow-stained nose
			Red-stained nose
	12	27 Oct 86	Red nasal discharge
			Hunched posture
			Tremors
			Moved stiffly
			Increased startle reflex
			Bloody hairball found under cage
			Euthanized in moribund condition

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F216	4	23 Oct 86	Small amount of feces Small black feces
	7	26 Oct 86	Small amount of feces Small black feces Yellow-stained nose Granular urine
	8	27 Oct 86	Nasal discharge
	10	29 Oct 86	Convulsions Injured bloody toenails
	11	30 Oct 86	Hair loss from groin Thick/foamy urine Strong rabbit/urine odor
	12	31 Oct 86	Orange-rust colored urine Twitching Red-stained yellowish granular material under cage Convulsions Loss of consciousness Mucus in nose Rapid/shallow respiration
	12-13	31 Oct-1 Nov 86	Red-stained paws Red-stained perianal Hypertonia
	13	1 Nov 86	Dehydrated Inactive Yellow-stained nose Strong rabbit/urine odor Cried out after dosing procedure
	14	2 Nov 86	Death
86F221	7	29 Oct 86	Yellow-stained nose
	8-19	30 Oct-10 Nov 86	Orange-rust colored urine Thick/foamy urine
	10-11	1-2 Nov 86	Diarrhea
	11	2 Nov 86	Brown material on hindpaws
	21-23	12-14 Nov 86	Orange-rust colored urine

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F228	0-3	20-23 Oct 86	Diarrhea
	5	25 Oct 86	Orange-rust colored urine
	6	26 Oct 86	Yellow-stained nose
	7	27 Oct 86	Diarrhea
	7-14	27 Oct-3 Nov 86	Granular/foamy urine
	8-20	28 Oct-9 Nov 86	Orange-rust colored urine
	12	1 Nov 86	Diarrhea
	15-19	4-8 Nov 86	Thick/foamy urine
	16	5 Nov 86	Diarrhea
	17	6 Nov 86	Orange-stained forepaw
	18	7 Nov 86	Diarrhea
86F229	5	25 Oct 86	Orange-rust colored urine
	6-7	26-27 Oct 86	Yellow-stained nose
	7	27 Oct 86	Red urine Red material in urine
	9	29 Oct 86	Convulsions Prostrate
	10	30 Oct 86	Moved stiffly Orange-rust colored urine Injured bloody toenails
	11	31 Oct 86	Death
86F233	5	26 Oct 86	Diarrhea
	9	30 Oct 86	Thick/foamy urine
	9-16	30 Oct-6 Nov 86	Orange-rust colored urine
	11-13	1-3 Nov 86	Diarrhea
	11-16	1-6 Nov 86	Thick/foamy urine
	14	4 Nov 86	Increase startle reflex
	18	8 Nov 86	Small amount of feces
	19	9 Nov 86	Increased salivation Mucus on nose Convulsions Prostrate Tremors No urine or feces under cage Red material under cage Death

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F240	7-10	30 Oct-2 Nov 86	Thick/foamy urine
	8-10	31 Oct-2 Nov 86	Orange-rust colored urine
	10-13	2-5 Nov 86	Diarrhea
	12	4 Nov 86	Orange-rust colored urine Thick/foamy urine
	14-19	6-11 Nov 86	Thick/foamy urine
	14-20	6-12 Nov 86	Orange-rust colored urine
	15	7 Nov 86	Diarrhea
	17-18	9-10 Nov 86	Diarrhea
	27	19 Nov 86	Diarrhea Deprived of water Small amount of feces
86F283	3-4	17-18 Jan 87	Diarrhea
	7-19	21 Jan-2 Feb 87	Orange-rust colored urine Thick/foamy urine
86F288	7-18	20-31 Jan 87	Thick/foamy urine
	9-14	22-27 Jan 87	Orange-rust colored urine
	16	29 Jan 87	Small amount of feces
	18	31 Jan 87	Orange-rust colored urine
	19	1 Feb 87	Red material under cage
	19-20	1-2 Feb 87	Small amount of feces
	20-24	2-6 Feb 87	Orange-rust colored urine
86F290	2-3	14-15 Jan 87	Diarrhea
	7-8	19-20 Jan 87	Mucus on feces
	8	20 Jan 87	Increased startle reflex
	8-17	20-29 Jan 87	Thick/foamy urine
	9-14	21-26 Jan 87	Orange-rust colored urine
	14-18	26-30 Jan 87	Diarrhea
	15-18	27-30 Jan 87	Brown material on abdomen and tail
	19	31 Jan 87	No feces/urine under cage
	20	1 Feb 87	Mucus on feces Clump of mucus under cage
	21	2 Feb 87	No feces/urine under cage
	23	4 Feb 87	Red urine
	23-25	4-6 Feb 87	Brown material on abdomen and tail

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F293	6-7	18-19 Jan 87	Thick/foamy urine
	8-13	20-25 Jan 87	Orange-rust colored urine
	9-11	21-23 Jan 87	Thick/foamy urine
	13	25 Jan 87	Thick/foamy urine
	14	26 Jan 87	Clear yellow urine
	14-16	26-28 Jan 87	Small amount of feces
	15	27 Jan 87	Orange-rust colored urine Thick/foamy urine Hunched posture Convulsions Injured bloody toenails Cyanosis
	15-16	27-28 Jan 87	Ataxia Hypertonia
	16	28 Jan 87	Euthanized in moribund condition
86F294	2	15 Jan 87	Diarrhea
	4	17 Jan 87	Diarrhea
	8-9	21-22 Jan 87	Thick/foamy urine
	11-19	24 Jan-1 Feb 87	Thick/foamy urine
	11-22	24 Jan-4 Feb 87	Orange-rust colored urine
	14	27 Jan 87	Diarrhea
86F296	7-19	26 Jan-7 Feb 87	Orange-rust colored urine Thick/foamy urine
	8	27 Jan 87	Hunched posture
	9	28 Jan 87	Hypertonia
	22	10 Feb 87	Orange-rust colored urine
86F302	7-16	20-29 Jan 87	Thick/foamy urine
	8	21 Jan 87	Diarrhea
	8-14	21-27 Jan 87	Orange-rust colored urine
	10-11	23-24 Jan 87	Brown material on forepaws
	11	24 Jan 87	Diarrhea
	13-15	26-28 Jan 87	Brown material on forepaws
	14	27 Jan 87	Diarrhea
	16	29 Jan 87	Diarrhea
	16-18	29-31 Jan 87	Orange-rust colored urine
	20-21	2-3 Feb 87	Small amount of feces
	23	5 Feb 87	Orange-rust colored urine
	28	10 Feb 87	Orange-rust colored urine

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F312	7-9	26-28 Jan 87	Thick/foamy urine
	9	28 Jan 87	Orange-rust colored urine
	13	1 Feb 87	No urine under cage
	14	2 Feb 87	Orange-rust colored urine
	14-15	2-3 Feb 87	Thick/foamy urine
	16	4 Feb 87	Red material under cage
	17	5 Feb 87	Small amount of urine
			Small amount of feces
	19	7 Feb 87	Yellow-stained nose
			Yellow-stained forepaws
			No feces under cage
			Deprived of water
	19-20	7-8 Feb 87	Hypertonia
	20	8 Feb 87	Small amount of feces
	22	10 Feb 87	Small amount of feces
	22-23	10-11 Feb 87	Orange-rust colored urine
86F315	7	26 Jan 87	Small amount of feces
	8	27 Jan 87	Thick/foamy urine
			Red material in urine
	8-9	27-28 Jan 87	Orange-rust colored urine
	9	28 Jan 87	Cool to touch
	10	29 Jan 87	Inactive
			Hunched posture
			Small amount of feces
			Hypertonia
	11	30 Jan 87	Death
86F317	5	26 Jan 87	Yellow-stained nose
	7-19	28 Jan-9 Feb 87	Thick/foamy urine
	7-29	28 Jan-19 Feb 87	Nasal discharge
	8	29 Jan 87	Orange-rust colored urine
	9	30 Jan 87	Small amount of feces
	10-17	31 Jan-7 Feb 87	Orange-rust colored urine
	11-12	1-2 Feb 87	Small amount of feces
	18-20	8-10 Feb 87	Small amount of feces
	27-28	17-18 Feb 87	Small amount of feces

Appendix G (Cont.): INDIVIDUAL MATERNAL CLINICAL SIGNS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Study Day(s)	Date(s)	Signs
86F319	7-12	27 Jan-1 Feb 87	Thick/foamy urine
	9-10	29-30 Jan 87	No feces under cage
	11	31 Jan 87	Hypertonia
	12-13	1-2 Feb 87	Small amount of feces
	12-14	1-3 Feb 87	Red stained nose and mouth
	13-14	2-3 Feb 87	Hypertonia
	15	4 Feb 87	Death

Appendix H
MATERNAL GROSS NECROPSY FINDINGS AT CESAREAN SECTION

Control Animals

Maternal ID	Finding
86F212	Dark red fallopian tubes Fragile uterus
86F218	Small, pale liver
86F231	Cyst on right fallopian tube Dark red right fallopian tube
86F235	Cysts on fallopian tubes Dark red fallopian tubes
86F297	Cysts on left fallopian tube
86F303	Dark red mass on pancreas
86F304	Cyst on right fallopian tube Two dark red masses on pancreas Slightly dilated renal pelvis of right kidney
86F309	Cyst on left fallopian tube
86F316	Cyst on right fallopian tube
86F321	Cyst on left fallopian tube Hard brown wart-like mass on liver

Appendix H(Cont.)
MATERNAL GROSS NECROPSY FINDINGS AT CESAREAN SECTION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Finding
86F202	Cysts on right fallopian tube Dark red fallopian tubes Two white spots on left kidney
86F225	Cyst on left fallopian tube Cavity adjacent to vessel in left kidney medulla Blotchy mottled liver
86F226	Dark red left fallopian tube
86F230	Dark spot on right ovary
86F232	Cysts on fallopian tubes Dark spot on left ovary
86F239	Dark red fallopian tubes
86F292	Cysts on fallopian tubes
86F300	Cyst on right fallopian tube
86F310	White spot in cortex of left kidney
86F311	Red mass in pancreas White/gray mass on lower lobe of left lung
86F320	Cysts on fallopian tubes Dark red mass on pancreas

Appendix H(Cont.)
MATERNAL GROSS NECROPSY FINDINGS AT CESAREAN SECTION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Finding
86F215	Cysts on fallopian tubes Red inflamed fallopian tubes
86F217	Cysts on fallopian tubes Dark red fallopian tubes Dark spot on left ovary
86F220	Dark red fallopian tubes
86F224	Cysts on fallopian tubes Dark red fallopian tubes
86F227	Cysts on fallopian tubes
86F234	Cyst on right fallopian tube
86F238	Dark red fallopian tubes
86F284	Cysts on right fallopian tube Dark spot on left ovary
86F285	Slightly dilated renal pelves of kidneys
86F313	Cysts on fallopian tubes
86F314	Cyst on right fallopian tube Three dark spots on pancreas Blotchy right kidney
86F322	Cyst on right fallopian tube

Appendix H(Cont.)
MATERNAL GROSS NECROPSY FINDINGS AT CESAREAN SECTION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Finding
86F221	Cysts in adipose tissue surrounding ovaries
86F228	Dark red fallopian tubes Blotchy liver
86F240	Cysts on right fallopian tube
86F288	Cyst on left fallopian tube
86F290	Cyst on left fallopian tube Pale kidneys
86F294	Cysts on fallopian tubes
86F302	Cysts on fallopian tubes Cavity adjacent to vessel in left kidney medulla Slightly dilated renal pelvis in right kidney
86F312	Dark red spot on pancreas Blotchy right kidney
86F317	60% of tissue in upper left lobe of lung necrotic, adhered to chest wall; 60% of tissue in middle lobe of right lung necrotic, cyst on lobe

Appendix I: INDIVIDUAL GESTATIONAL DATA

Control Animals

Maternal ID	Corpora Lutea	Implant	% Implant*	Resorp-tions	% Resorp-tions†	Number of Fetuses			
						Dead	% Dead§	Live	% Live«
86F212	8	8	100	0	0	0	0	8	100
86F214	11	9	82	1	11	0	0	8	100
86F218	14	10	71	0	0	0	0	10	100
86F231	14	13	93	1	8	0	0	12	100
86F235	10	10	100	0	0	0	0	10	100
86F236	10	8	80	0	0	0	0	8	100
86F237	8	8	100	0	0	0	0	8	100
86F297	10	9	90	0	0	0	0	9	100
86F303	8	8	100	0	0	0	0	8	100
86F304	10	10	100	0	0	0	0	10	100
86F309	11	11	100	1	9	0	0	10	100
86F316	11	11	100	0	0	0	0	11	100
86F321	9	9	100	0	0	0	0	9	100

*[implantations per litter/corpora lutea per litter] x 100
†[resorptions per litter/implantations per litter] x 100
§[dead fetuses per litter/live + dead fetuses per litter] x 100
«[live fetuses per litter/live + dead fetuses per litter] x 100

Appendix I(Cont.): INDIVIDUAL GESTATIONAL DATA

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Corpora Lutea	Implant	% Implant*	Resorp-tions	% Resorp-tionst	Number of Fetuses			
						Dead	% Dead§	Live	% Live«
86F202	8	8	100	1	13	0	0	7	100
86F203	13	11	85	1	9	1	10	9	90
86F210	10	10	100	1	10	0	0	9	100
86F225	9	9	100	0	0	0	0	9	100
86F226	7	7	100	1	14	0	0	6	100
86F230	7	7	100	1	14	0	0	6	100
86F232	12	12	100	1	8	0	0	11	100
86F239	12	11	92	1	9	0	0	10	100
86F292	13	12	92	1	8	0	0	11	100
86F295	16	10	63	2	20	0	0	8	100
86F300	12	11	92	1	9	0	0	10	100
86F308	12	11	92	1	9	0	0	10	100
86F310	13	13	100	1	8	2	17	10	83
86F311	11	11	100	1	9	0	0	10	100
86F320	13	10	77	0	0	1	10	9	90

*[implantations per litter/corpora lutea per litter] x 100
†[resorptions per litter/implantations per litter] x 100
§[dead fetuses per litter/live + dead fetuses per litter] x 100
«[live fetuses per litter/live + dead fetuses per litter] x 100

Appendix I(Cont.): INDIVIDUAL GESTATIONAL DATA

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Corpora Lutea	Implant	% Implant*	Resorp-tions	% Resorp-tions†	Number of Fetuses			
						Dead	% Dead§	Live	% Live«
86F215	11	8	73	1	13	0	0	7	100
86F217	15	12	80	1	8	0	0	11	100
86F220	11	10	91	1	10	0	0	9	100
86F223	12	10	83	0	0	0	0	10	100
86F224	12	12	100	0	0	0	0	12	100
86F227	10	10	100	1	10	0	0	9	100
86F234	10	9	90	0	0	0	0	9	100
86F238	9	9	100	0	0	1	11	8	89
86F284	12	8	67	0	0	0	0	8	100
86F285	8	8	100	1	13	0	0	7	100
86F298	10	10	100	0	0	0	0	10	100
86F301	10	9	90	0	0	0	0	9	100
86F313	11	10	91	2	20	0	0	8	100
86F314	13	4	31	1	25	0	0	3	100
86F322	12	11	92	0	0	0	0	11	100

*[implantations per litter/corpora lutea per litter] x 100
†[resorptions per litter/implantations per litter] x 100
§[dead fetuses per litter/live + dead fetuses per litter] x 100
«[live fetuses per litter/live + dead fetuses per litter] x 100

Appendix I(Cont.): INDIVIDUAL GESTATIONAL DATA

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Corpora Lutea	Implant	% Implant*	Resorp-tions	% Resorp-tions†	Number of Fetuses			
						Dead	% Dead§	Live	% Live«
86F221	10	9	90	0	0	0	0	9	100
86F228	9	9	100	0	0	0	0	9	100
86F240	12	10	83	0	0	0	0	10	100
86F283	12	12	100	0	0	1	8	11	92
86F288	13	11	85	1	9	1	10	9	90
86F290	8	8	100	8	100	0		0	
86F294	10	10	100	4	40	0	0	6	100
86F296	10	10	100	0	0	0	0	10	100
86F302	12	6	50	2	33	0	0	4	100
86F312	14	13	93	2	15	0	0	11	100
86F317	8	8	100	0	0	0	0	8	100

*[implantations per litter/corpora lutea per litter] x 100
†[resorptions per litter/implantations per litter] x 100
§[dead fetuses per litter/live + dead fetuses per litter] x 100
«[live fetuses per litter/live + dead fetuses per litter] x 100

Appendix J: FETAL SEX, WEIGHT, AND LENGTH

Control Animals

Maternal ID	No.	Sex			Mean Weight (g) ± S.D.		Mean Length (cm) ± S.D.	
		M	F	M %	Males	Females	Males	Females
86F212	8	5	3	63	44.3 ± 2.1	43.7 ± 3.6	10.3 ± 0.3	10.3 ± 0.3
86F214	8	0	8	0		45.4 ± 5.1		10.1 ± 0.4
86F218	10	6	4	60	39.8 ± 3.4	40.4 ± 6.8	10.1 ± 0.3	10.1 ± 0.7
86F231	12	3	9	25	43.2 ± 4.1	35.9 ± 3.4	10.2 ± 0.3	9.8 ± 0.3
86F235	10	8	2	80	43.0 ± 6.3	46.2 ± 4.5	10.3 ± 0.5	10.6 ± 0.6
86F236	8	2	6	25	46.4 ± 3.1	50.8 ± 3.1	10.4 ± 0.1	10.9 ± 0.3
86F237	8	4	4	50	35.1 ± 3.9	37.4 ± 3.4	10.0 ± 0.2	10.0 ± 0.3
86F297	9	4	5	44	44.0 ± 3.2	43.4 ± 5.4	10.8 ± 0.2	10.5 ± 0.4
86F303	8	3	5	38	45.9 ± 7.7	42.9 ± 7.1	10.6 ± 0.5	10.6 ± 0.6
86F304	10	6	4	60	44.3 ± 7.3	44.9 ± 7.8	10.8 ± 0.5	10.6 ± 0.6
86F309	10	2	8	20	45.0 ± 9.0	44.2 ± 3.4	10.7 ± 0.5	10.9 ± 0.3
86F316	11	7	4	64	41.9 ± 4.2	44.1 ± 6.2	10.5 ± 0.2	10.5 ± 0.8
86F321	9	2	7	22	41.0 ± 3.8	45.3 ± 4.3	10.9 ± 0.4	11.3 ± 0.4

Appendix J(Cont.): FETAL SEX, WEIGHT, AND LENGTH

100 mg/kg/day Nitroguanidine Animals

Maternal ID	No.	Sex			Mean Weight (g) ± S.D.		Mean Length (cm) ± S.D.	
		M	F	M %	Males	Females	Males	Females
86F202	7	2	5	29	50.6 ± 4.3	42.6 ± 3.2	10.2 ± 0.6	9.8 ± 0.3
86F203	9	2	7	22	43.4 ± 0.2	44.6 ± 5.0	10.2 ± 0.4	10.0 ± 0.4
86F210	9	3	6	33	47.5 ± 8.6	46.3 ± 5.1	10.3 ± 0.5	10.3 ± 0.3
86F225	9	5	4	56	39.5 ± 2.1	38.1 ± 5.2	10.1 ± 0.2	9.7 ± 0.3
86F226	6	5	1	83	46.2 ± 2.4	48.3	10.2 ± 0.1	10.1
86F230	6	1	5	17	46.2	43.8 ± 2.9	10.8	10.3 ± 0.2
86F232	11	7	4	64	36.5 ± 9.5	34.2 ± 7.8	9.8 ± 0.8	9.5 ± 0.6
86F239	10	6	4	60	39.9 ± 8.9	38.2 ±10.6	10.3 ± 0.7	10.1 ± 0.9
86F292	11	5	6	45	40.2 ± 6.8	43.7 ± 5.8	10.5 ± 0.5	10.8 ± 0.4
86F295	8	5	3	63	45.9 ± 3.5	45.3 ± 2.7	11.1 ± 0.3	11.1 ± 0.2
86F300	10	3	7	30	40.0 ± 6.3	42.5 ± 5.5	10.8 ± 0.6	10.7 ± 0.4
86F308	10	8	2	80	34.5 ± 5.5	31.4 ± 0.1	10.2 ± 0.4	9.9 ± 0.1
86F310	10	6	4	60	34.4 ± 4.1	29.3 ± 4.1	10.0 ± 0.4	9.9 ± 0.4
86F311	10	4	6	40	40.3 ± 2.7	38.3 ± 2.8	10.9 ± 0.1	10.8 ± 0.3
86F320	9	4	5	44	50.7 ± 2.3	45.7 ± 3.0	11.3 ± 0.7	11.2 ± 0.3

Appendix J(Cont.): FETAL SEX, WEIGHT, AND LENGTH

316 mg/kg/day Nitroguanidine Animals

Maternal ID	No.	Sex			Mean Weight(g) ± S.D.		Mean Length(cm) ± S.D.	
		M	F	M %	Males	Females	Males	Females
86F215	7	4	3	57	49.2 ± 9.2	48.7 ± 5.9	10.5 ± 0.4	10.3 ± 0.4
86F217	11	7	4	64	43.7 ± 7.7	42.4 ± 3.6	10.1 ± 0.7	10.2 ± 0.2
86F220	9	2	7	22	43.6 ± 0.6	45.1 ± 6.9	10.3 ± 0.4	9.9 ± 0.4
86F223	10	3	7	30	40.2 ± 0.9	38.8 ± 6.2	10.0 ± 0.2	9.9 ± 0.5
86F224	12	5	7	42	33.9 ± 1.8	28.0 ± 5.7	9.7 ± 0.3	9.2 ± 0.6
86F227	9	4	5	44	44.6 ± 4.8	41.2 ± 4.1	10.4 ± 0.3	10.1 ± 0.3
86F234	9	3	6	33	47.1 ± 3.5	42.1 ± 4.3	11.0 ± 0.2	10.5 ± 0.5
86F238	8	4	4	50	47.6 ± 1.1	44.2 ± 2.5	11.1 ± 0.3	10.6 ± 0.4
86F284	8	5	3	63	51.0 ± 4.4	49.1 ± 9.1	11.3 ± 0.5	11.4 ± 1.0
86F285	7	4	3	57	44.8 ± 2.5	40.3 ± 2.6	10.9 ± 0.1	10.4 ± 0.3
86F298	10	6	4	60	39.0 ± 5.3	41.4 ± 7.5	10.4 ± 0.5	10.6 ± 0.6
86F301	9	6	3	67	45.5 ± 5.8	41.8 ± 2.3	10.9 ± 0.4	10.8 ± 0.3
86F313	8	1	7	13	40.9	37.7 ± 4.3	10.5	10.6 ± 0.4
86F314	3	1	2	33	46.4	45.9 ± 3.3	11.3	11.2 ± 0.3
86F322	11	3	8	27	36.5 ± 6.1	33.1 ± 5.2	9.9 ± 0.5	10.0 ± 0.5

Appendix J(Cont.): FETAL SEX, WEIGHT, AND LENGTH

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	No.	Sex			Mean Weight (g) ± S.D.		Mean Length (cm) ± S.D.	
		M	F	M %	Males	Females	Males	Females
86F221	9	4	5	44	44.6 ± 3.9	48.2 ± 4.6	10.6 ± 0.4	10.5 ± .5
86F228	9	3	6	33	34.6 ± 5.7	34.9 ± 2.1	9.1 ± 0.5	9.4 ± .3
86F240	10	5	5	50	41.3 ± 7.6	34.2 ± 4.1	10.3 ± 0.7	9.8 ± .6
86F283	11	5	6	45	33.9 ± 6.0	32.5 ± 6.6	9.8 ± 0.5	9.8 ± .7
86F288	9	3	6	33	37.1 ± 9.3	36.9 ± 6.2	10.1 ± 1.0	10.1 ± .6
86F294	6	2	4	33	31.3 ± 0.7	37.0 ± 6.2	9.7 ± 0.1	10.3 ± .4
86F296	10	5	5	50	44.7 ± 5.3	42.2 ± 2.7	10.9 ± 0.4	10.5 ± .3
86F302	4	3	1	75	45.1 ± 3.0	40.8	10.4 ± 0.1	10.3
86F312	11	5	6	45	33.4 ± 5.3	31.3 ± 3.6	10.0 ± 0.7	9.7 ± .4
86F317	8	5	3	63	23.8 ± 4.0	23.5 ± 3.6	8.8 ± 0.8	8.7 ± .6

Appendix K: FETAL EXTERNAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F212	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F214	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F218	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F231	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	L	Normal	Normal
	M	Normal	Normal
86F235	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F236	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F237	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F297	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
[illegible]	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F304	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F309	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
86F316	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F321	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F202	A	Normal	Normal
	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F203	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F210	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F225	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	
86F226	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	
86F230	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F232	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
86F239	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F292	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
86F295	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F300	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F308	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Ectrodactyly; hindpaws, 2 toes present on left, 3 toes present on right
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F310	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	M	Normal	Normal
86F311	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F320	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	J	Normal	

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F215	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F217	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F220	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F223	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F224	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
86F227	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	J	Normal	Normal

Appandix K (Cont.): FETAL EXTERNAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
8eF234	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
8eF138	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
8eF284	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F285	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F298	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F301	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F313	A	Normal	Normal
	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F314	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
86F322	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F221	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F228	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F240	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F283	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F288	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	K	Normal	Normal
86F294	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F296	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix K (Cont.): FETAL EXTERNAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F302	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
86F312	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
	M	Normal	Normal
86F317	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Cleft palate
	E	Normal	Normal
	F	Normal	Normal
	G	Bloated abdomen	Normal
	H	Normal	Normal

Appendix L: FETAL VISCERAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F212	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F214	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F218	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F231	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	L	Normal	Normal
	M	Normal	Normal
86F235	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	[illegible]	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F236	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F237	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F297	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F303	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F304	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F309	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
86F316	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F321	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F202	A	Normal	Normal
	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F203	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F210	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F225	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	
86F226	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Dilated renal pelvis	
86F230	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F232	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
86F239	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F292	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
86F295	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F300	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F308	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F310	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	M	Normal	Normal
86F311	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F320	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
			Normal
86F215	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	
			Normal
86F217	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F220	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F223	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F224	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
86F227	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F234	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F238	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F284	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F285	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F298	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Elongated ovaries	Normal
86F301	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F313	A	Normal	Normal
	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F314	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
86F322	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Dilated renal pelvis	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

1000 mg/kg/day Nitroquanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F221	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
86F228	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F240	A	Norm	Normal
	B	Norma	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F283	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F288	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	K	Normal	Normal
86F294	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F296	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix L (Cont.): FETAL VISCERAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F302	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
86F312	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal
	M	Normal	Normal
86F317	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Cleft palate Left ureter transversed midline, ran adjacent to right ureter
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Enlarged left heart ventricle	Normal

Appendix M: FETAL SKELETAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F212	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Dot of ossification adjacent to 7th cervical vertebra Sternebra misshaped 5 sternebrae ossified	Normal
	F	5 sternebrae ossified	Normal
	G	Normal	Normal
	H	Sternebra split Sternebrae scrambled	
86F214	A	14 phalanges right forepaw ossified	Normal
	B	Normal	Normal
	C	5 sternebrae ossified	Normal
	D	14 phalanges/forepaw ossified	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	5 sternebrae ossified	Normal
	I	Sternebra dumbbell shaped	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F218	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	5 st. ified	Normal
	I	Normal	Normal
	J	Normal	Normal
86F231	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Patella not ossified	Normal
	E	5 sternebrae ossified Sternebra partially ossified	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	5 sternebrae ossified	Normal
	J	5 sternebrae ossified	Normal
	L	Normal	Normal
	M	Dots of ossification above 1st sternebra	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F235	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Patellae not ossified	Normal
	E	Patella not ossified	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Patella not ossified	Normal
	I	Normal	Normal
	J	Normal	Normal
86F236	A	Sternebra partially ossified	Normal
	B	Sternebra partially ossified	Normal
	C	Normal	Normal
	D	5 sternebrae ossified	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	5 sternebrae ossified	Normal
	H	Sternebra partially ossified	Normal
86F237	A	Normal	Normal
	B	Patella not ossified	Normal
	C	Patellae not ossified	Normal
	D	Dots of os ification above 1st sterne'ia	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F297	A	5 sternebrae ossified	Normal
	B	Sternebra partially ossified	Normal
	C	Normal	Normal
	D	Sternebra split Sternebrae diagonally ossified	Normal
	E	Normal	Normal
	F	5 sternebrae ossified 14 phalanges right forepaw ossified	Normal
	G	Sternebra split	Normal
	H	Sternebra split	Normal
	I	Sternebra partially ossified	Normal
86F303	A	Normal	Normal
	B	Normal	Normal
	C	Sternebra split	Normal
	D	Sternebra split	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F304	A	Dots of ossification above 1st sternebra	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F309	A	Sternebra dumbbell shaped	Normal
	B	Sternebra partially ossified 14 phalanges right forepaw ossified 13 phalanges left forepaw ossified	Normal
	C	Sternebra partially ossified	Normal
	D	Sternebrae diagonally ossified Sternebra misshaped	Normal
	E	5 sternebrae ossified 14 phalanges/forepaw ossified	Normal
	F	14 phalanges/forepaw ossified	Normal
	H	5 sternebrae ossified	Normal
	I	5 sternebrae ossified 14 phalanges/forepaw ossified	Normal
	J	Sternebra partially ossified	Normal
	K	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

Control Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F316	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
86F321	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Olecranon not ossified	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Sternebra partially ossified	Normal
	I	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F202	A	Normal	Normal
	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F203	A	5 sternebrae ossified	Normal
	B	14 phalanges left forepaw ossified	Normal
		Patellae not ossified	Normal
	C	Normal	Normal
	D	Sternebra partially ossified	Normal
	F	5 sternebrae ossified	Normal
	G	5 sternebrae ossified	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F210	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F225	A	5 sternebrae ossified	Normal
	B	5 sternebrae ossified	Normal
	C	5 sternebrae ossified 11 phalanges/forepaw ossified 11 phalanges/hindpaw ossified Olecranon not ossified	Normal
	D	Sternebra partially ossified	Normal
	E	5 sternebrae ossified Olecranons not ossified Patellae not ossified	Normal
	F	Sternebra split	Normal
	G	Sternebra partially ossified	Normal
	H	Sternebra partially ossified	Normal
	I	5 sternebrae ossified	Normal
86F226	A	Sternebra dumbbell shaped	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
86F230	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	5 sternebrae ossified 14 phalanges/forepaw ossified	Normal
	G	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F232	A	Sternebra partially ossified	Normal
	B	5 sternebrae ossified	Normal
	C	Dot of ossification adjacent to 7th cervical vertebra 5 sternebrae ossified	Normal
	D	5 sternebrae ossified 14 phalanges/forepaw ossified	Normal
	E	Sternebra misshaped and partially ossified	Normal
	F	5 sternebrae ossified 14 phalanges right forepaw ossified 13 phalanges left forepaw ossified Olecranons not ossified Patella not ossified	Normal
	G	5 sternebrae ossified 12 phalanges/forepaw ossified 11 phalanges/hindpaw ossified Olecranons not ossified Patellae not ossified	Normal
	I	Sternebra partially ossified 14 phalanges/forepaw ossified Olecranons not ossified	Normal
	J	Sternebra partially ossified Olecranon not ossified	Normal
	K	Sternebra partially ossified 14 phalanges right forepaw ossified Olecranon not ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F232(Cont)	L	5 sternebrae ossified Dot of ossification above 1st sternebra	Normal
86F239	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	14 phalanges/forepaw ossified Olecranons not ossified Patellae not ossified	Normal
	G	5 sternebrae ossified 21 vertebrae (thoracic, lumbar, and sacral)	Normal
	H	14 phalanges/forepaw ossified Olecranons not ossified Patellae not ossified	Normal
	I	14 phalanges/forepaw ossified Olecranons not ossified Patellae not ossified	Normal
	J	Normal	Normal
	K	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F292	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Dot of ossification adjacent to 7th cervical vertebra	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Sternebra partially ossified	Normal
	J	sternebrae ossified	Normal
	K	Normal	Normal
	L	Normal	Normal
86F295	B	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Sternebra split	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F300	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	4 sternebrae ossified	Normal
		14 phalanges/forepaw ossified	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	14 phalanges/forepaw ossified	Normal
		Patella not ossified	
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F308	A	Normal	Normal
	B	Olecranons not ossified	Normal
	C	Olecranons not ossified Patellae not ossified 14 phalanges right forepaw ossified	Ectrodactyly: right hindpaw, 1 metatarsal and 4 phalanges absent; left hindpaw, 1 metatarsal and 7 phalanges absent: left forepaw, 3 phalanges of pollex absent
	D	Normal	Normal
	E	Sternebra partially ossified 14 phalanges/forepaw ossified	Normal
	F	Normal	Normal
	G	Olecranons not ossified Patellae not ossified	Normal
	H	Olecranons not ossified Patellae not ossified	Normal
	J	Olecranon not ossified Patella not ossified	Normal
	K	Sternebra partially ossified Sternebra split Patellae not ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F310	A	Sternebra partially ossified	Normal
	B	5 sternebrae ossified 14 phalanges/forepaw ossified	Normal
	C	Dot of ossification adjacent to 7th cervical vertebra Sternebra partially ossified	Normal
	E	Normal	Normal
	G	Sternebra partially ossified Sternebra split Patellae not ossified	Normal
	H	Normal	Normal
	I	4 sternebrae ossified	Normal
	J	Normal 14 phalanges left forepaw ossified	Normal
	K	14 phalanges/forepaw ossified	Normal
	M	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F311	A	Normal	Normal
	B	5 sternebrae ossified	Normal
	C	Normal	Normal
	D	Dot of ossification adjacent to 7th cervical vertebra Sternebra partially ossified	Normal
	E	Dot of ossification adjacent to 7th cervical vertebra Sternebra partially ossified	Normal
	F	Dot of ossification adjacent to 7th cervical vertebra 5 sternebrae ossified	Normal
	H	Sternebra partially ossified	Normal
	I	Dot of ossification adjacent to 7th cervical vertebra Sternebra partially ossified 14 phalanges/forepaw ossified	Normal
	J	Normal	Normal
	K	5 sternebrae ossified	Normal
86F320	A	Sternebra partially ossified	Normal
	B	Normal	Normal
	C	Sternebra partially ossified	Normal
	D	Normal	Normal
	E	Sternebra partially ossified	Normal
	F	Sternebra partially ossified	Normal
	G	Sternebra partially ossified	Normal
	H	Normal	Normal
	J	Sternebrae diagonally ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F215	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
86F217	A	Normal	Normal
	B	Normal	Normal
	C	5 sternebrae ossified	Normal
	D	Normal	Normal
	E	5 sternebrae ossified	Normal
	G	Sutural bone 5 sternebrae ossified 13 phalanges/forepaw ossified Patellae not ossified	Normal
	H	Normal	Normal
	I	5 sternebrae ossified	Normal
	J	5 sternebrae ossified	Normal
	K	Normal	Normal
	L	5 sternebrae ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F220	A	5 sternebrae ossified	Normal
	B	5 sternebrae ossified 14 phalanges/forepaw ossified	Normal
	C	5 sternebrae ossified	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	5 sternebrae ossified 14 phalanges left forepaw ossified	Normal
	J	Normal	Normal
86F223	A	5 sternebrae ossified	Normal
	B	5 sternebrae ossified	Normal
	C	5 sternebrae ossified	Normal
	D	Sternebra partially ossified	Normal
	E	5 sternebrae ossified	Normal
	F	5 sternebrae ossified	Normal
	G	5 sternebrae ossified Olecranon not ossified	Normal
	H	5 sternebrae ossified	Normal
	I	5 sternebrae ossified	Normal
	J	Sternebra partially ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F224	A	14 phalanges/forepaw ossified Olecranons not ossified Patellae not ossified	Normal
	B	5 sternebrae ossified	Normal
	C	5 sternebrae ossified 14 phalanges right forepaw ossified	Normal
	D	Sternebra partially ossified 14 phalanges/forepaw ossified	Normal
	E	5 sternebrae ossified 14 phalanges/forepaw ossified Olecranons not ossified Patellae not ossified	Normal
	F	13 phalanges/forepaw ossified Olecranons not ossified Patella not ossified	Normal
	G	5 sternebrae ossified Sternebra split 13 phalanges/forepaw ossified Olecranons not ossified Patellae not ossified 11 phalanges/hindpaw ossified	Normal
	H	4 sternebrae ossified Olecranons not ossified	Normal
	I	5 sternebrae ossified 14 phalanges/forepaw ossified Olecranons not ossified Patella not ossified	Normal
	J	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F224(Cont)	K	14 phalanges/forepaw ossified Olecranons not ossified	Normal
	L	5 sternebrae ossified	Normal
86F227	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	J	5 sternebrae ossified	Normal
86F234	A	Normal	Normal
	B	Sternebra partially ossified	Normal
	C	Sternebra partially ossified Sternebra dumbbell shaped Patellae not ossified	Normal
	D	Normal	Normal
	E	14 phalanges left forepaw ossified	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F238	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	5 sternebrae ossified	Normal
	I	Sternebra partially ossified	Normal
86F284	A	Normal	Normal
	B	Sternebra partially ossified	Normal
	C	Normal	Normal
	D	Sternebra partially ossified	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	5 sternebrae ossified	Normal
	H	Normal	Normal
86F285	A	Normal	Normal
	C	Normal	Normal
	D	Normal	Normal
	E	Sternebra partially ossified	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Ribs (left 6 and 7) short, not parallel	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F298	A	Normal	Normal
	B	Normal	Normal
	C	Coccygeal vertebrae misaligned	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Normal	Normal
86F301	A	Sternebra split	Normal
	B	Normal	Normal
	C	Sternebra partially ossified	Normal
	D	Sternebra partially ossified	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Sternebra partially ossified	Normal
	H	Normal	Normal
	I	5 sternebrae ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F313	A	Olecranons not ossified Patellae not ossified	Normal
	B	Sternebra partially ossified	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	Sternebra partially ossified 13 phalanges/forepaw ossified	Normal
	G	Sternebra diagonally ossified 14 phalanges/forepaw ossified	Normal
	H	Sternebrae diagonally ossified Patellae not ossified	Normal
	I	Normal	Normal
86F314	A	Sternebra partially ossified	Normal
	C	Sternebra partially ossified	Normal
	D	Sternebrae partially ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F322	A	Normal	Normal
	B	Normal	Normal
	C	Sternebra partially ossified	Normal
	D	Normal	Normal
	E	Sternebra partially ossified	Normal
	F	Normal	Normal
	G	14 phalanges/forepaw ossified Patella not ossified	Normal
	H	Normal	Normal
	I	Normal	Normal
	J	Sternebra partially ossified	Normal
	K	5 sternebrae ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F221	A	Normal	Normal
	B	Normal	Normal
	C	5 sternebrae ossified	Normal
	D	Mid section of 13th ribs not ossified Sternebra split	Normal
	E	5 sternebrae ossified	Normal
	F	Sternebra partially ossified	Normal
	G	5 sternebrae ossified	Normal
	H	Normal	Normal
	I	Normal	Normal
86F228	A	Sternebra partially ossified Olecranons not ossified Patella not ossified	Normal
	B	Sternebra partially ossified Olecranons not ossified	Normal
	C	Sternebra partially ossified Olecranons not ossified 14 phalanges/forepaw ossified	Normal
	D	Olecranons not ossified	Normal
	E	Olecranons not ossified	Normal
	F	Olecranons not ossified	Normal
	G	Olecranons not ossified	Normal
	H	Olecranons not ossified	Normal
	I	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

1000 mg/kg/day Nitroguanidi Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F240	A	Normal	Normal
	B	Normal	Normal
	C	Sternebra partially ossified	Normal
	D	Normal	Normal
	E	Normal	Normal
	F	5 sternebrae ossified	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Sternebra partially ossified	Normal
	J	Normal	Normal
86F283	A	Normal	Normal
	B	14 phalanges/forepaw ossified	Normal
	C	Normal	Normal
	D	14 phalanges/forepaw ossified	Normal
	F	5 sternebrae ossified	Normal
	G	Normal	Normal
	H	14 phalanges/forepaw ossified	Normal
	I	Normal	Normal
	J	Normal	Normal
	K	Normal	Normal
	L	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F288	A	Normal	Normal
	C	Normal	Normal
	D	14 phalanges/forepaw ossified	Normal
	E	5 sternebrae ossified	Normal
	F	Sternebra partially ossified	Normal
	G	Sternebra misshaped Olecranons not ossified Patellae not ossified	Normal
	H	5 sternebrae ossified Left 12th vertebral arch, centra, and left 12th rib not ossified Olecranons not ossified Patella not ossified	Normal
	I	Sternebra split Olecranons not ossified	Normal
	K	Metacarpal misaligned Olecranons not ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F294	A	5 sternebrae ossified	Normal
	B	Sternebra partially ossified 14 phalanges/forepaw ossified Olecranons not ossified 11 phalanges/hindpaw ossified Patellae not ossified	Normal
	C	5 sternebrae ossified	Normal
	H	5 sternebrae ossified Sternebra partially ossified Sternebrae diagonally ossified 14 phalanges/forepaw ossified Patellae not ossified	Normal
	I	5 sternebrae ossified Patellae not ossified	Normal
	J	5 sternebrae ossified Patellae not ossified	Normal
86F296	A	Normal	Normal
	B	Normal	Normal
	C	Normal	Normal
	D	Sternebra partially ossified	Normal
	E	Sternebra partially ossified	Normal
	F	Sternebra dumbbell shaped	Normal
	G	Normal	Normal
	H	Normal	Normal
	I	Sternebra partially ossified	Normal
	J	Normal	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F302	A	Normal	Normal
	C	Normal	Normal
	D	Sutural bone	Normal
	F	Normal	Normal
86F312	A	Normal	Normal
	C	Sternebrae fused	Normal
	D	14 phalanges/forepaw ossified	Normal
	E	Normal	Normal
	F	Normal	Normal
	G	Normal	Normal
	H	Patellae not ossified	Normal
	I	Sternebra partially ossified	Normal
	K	Normal	Normal
	L	Normal	Normal
	M	14 phalanges left forepaw ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F317	A	Sternebrae diagonally ossified 13 phalanges/forepaw ossified 11 phalanges right hindpaw ossified Patella not ossified	Normal
	B	5 sternebrae ossified 13 phalanges right forepaw ossified 12 phalanges left forepaw ossified Pubis not ossified Olecranons not ossified Patellae not ossified	Normal
	C	13 phalanges/forepaw ossified 11 phalanges/hindpaw ossified Pubis not ossified Olecranons not ossified Patellae not ossified	Normal
	D	Sternebra partially ossified 5 sternebrae ossified 13 phalanges/forepaw ossified Pubis not ossified Olecranons not ossified Patellae not ossified	Cleft palate
	E	5 sternebrae ossified Sternebra partially ossified 14 phalanges/forepaw ossified 11 phalanges/hindpaw ossified Patellae not ossified	Normal

Appendix M (Cont.): FETAL SKELETAL EXAMINATION

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Fetal ID	Description of Variation	Description of Malformation
86F317	F	4 sternebrae ossified 11 phalanges/forepaw ossified 11 phalanges/hindpaw ossified Olecranons not ossified Pubis not ossified Patellae not ossified	Normal
	G	5 sternebrae ossified 14 phalanges/forepaw ossified	Normal
	H	13 phalanges/forepaw ossified	Normal

Appendix N: INCIDENCE OF FETAL EXAMINATION FINDINGS

Control Animals

Maternal ID	Number Examined	External				Visceral				Skeletal			
		Malformed		Variants		Malformed		Variants		Malformed		Variants	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
86F212	8	0	0	0	0	0	0	0	0	0	0	3	38
86F214	8	0	0	0	0	0	0	0	0	0	0	5	63
86F218	10	0	0	0	0	0	0	0	0	0	0	1	10
86F231	12	0	0	0	0	0	0	0	0	0	0	5	42
86F235	10	0	0	0	0	0	0	0	0	0	0	3	30
86F236	8	0	0	0	0	0	0	0	0	0	0	5	63
86F237	8	0	0	0	0	0	0	0	0	0	0	3	38
86F297	9	0	0	0	0	0	0	0	0	0	0	7	78
86F303	8	0	0	0	0	0	0	0	0	0	0	2	25
86F304	10	0	0	0	0	0	0	0	0	0	0	1	10
86F309	10	0	0	0	0	0	0	0	0	0	0	9	90
86F316	11	0	0	0	0	0	0	0	0	0	0	0	0
86F321	9	0	0	0	0	0	0	0	0	0	0	2	22

Appendix N(Cont.): INCIDENCE OF FETAL EXAMINATION FINDINGS

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Number Examined	External				Visceral				Skeletal			
		Malformed		Variants		Malformed		Variants		Malformed		Variants	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
86F202	7	0	0	0	0	0	0	0	0	0	0	0	0
86F203	9	0	0	0	0	0	0	0	0	0	0	5	56
86F210	9	0	0	0	0	0	0	0	0	0	0	0	0
86F225	9	0	0	0	0	0	0	0	0	0	0	9	100
86F226	6	0	0	0	0	0	0	1	17	0	0	1	17
86F230	6	0	0	0	0	0	0	0	0	0	0	1	17
86F232	11	0	0	0	0	0	0	0	0	0	0	11	100
86F239	10	0	0	0	0	0	0	0	0	0	0	4	40
86F292	11	0	0	0	0	0	0	0	0	0	0	3	27
86F295	8	0	0	0	0	0	0	0	0	0	0	1	13
86F300	10	0	0	0	0	0	0	0	0	0	0	2	20
86F308	10	1	10	0	0	0	0	0	[illegible]	1	10	7	70
86F310	10	0	0	0	0	0	0	0	[illegible]	0	0	7	70
86F311	10	0	0	0	0	0	0	0	[illegible]	0	0	7	70
86F320	9	0	0	0	0	0	0	0	0	0	0	6	67

Appendix N(Cont.): INCIDENCE OF FETAL EXAMINATION FINDINGS

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Number Examined	External				Visceral				Skeletal			
		Malformed		Variants		Malformed		Variants		Malformed		Variants	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
86F215	7	0	0	0	0	0	0	0	0	0	0	0	-
86F217	11	0	0	0	0	0	0	0	0	0	0	6	55
86F220	9	0	0	0	0	0	0	0	0	0	0	4	44
86F223	10	0	0	0	0	0	0	0	0	0	0	10	100
86F224	12	0	0	0	0	0	0	0	0	0	0	11	92
86F227	9	0	0	0	0	0	0	0	0	0	0	1	11
86F234	9	0	0	0	0	0	0	0	0	0	0	3	33
86F238	8	0	0	0	0	0	0	0	0	0	0	2	25
86F284	8	0	0	0	0	0	0	0	0	0	0	3	38
86F285	7	0	0	0	0	0	0	0	0	0	0	2	29
86F298	10	0	0	0	0	0	0	1	10	0	0	1	10
86F301	9	0	0	0	0	0	0	0	0	0	0	5	56
86F313	8	0	0	0	0	0	0	0	0	0	0	5	63
86F314	3	0	0	0	0	0	0	0	0	0	0	3	100
86F322	11	0	0	0	0	0	0	1	9	0	0	5	45

Appendix N(Cont.): INCIDENCE OF FETAL EXAMINATION FINDINGS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Number Examined	External				Visceral				Skeletal			
		Malformed		Variants		Malformed		Variants		Malformed		Variants	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
86F221	9	0	0	0	0	0	0	0	0	0	0	5	56
86F228	9	0	0	0	0	0	0	0	0	0	0	9	100
86F240	10	0	0	0	0	0	0	0	0	0	0	3	30
86F283	11	0	0	0	0	0	0	0	0	0	0	4	36
86F288	9	0	0	0	0	0	0	0	0	0	0	7	78
86F294	6	0	0	0	0	0	0	0	0	0	0	6	100
86F296	10	0	0	0	0	0	0	0	0	0	0	4	40
86F302	4	0	0	0	0	0	0	0	0	0	0	1	25
86F312	11	0	0	0	0	0	0	0	0	0	0	5	45
86F317	8	1	13	1	13	1	13	1	13	1	13	8	100

Appendix O

INCIDENCE OF FETAL MALFORMATIONS AND VARIATIONS

Control Animals

Maternal ID	Number Examined	Malformed No.	Malformed %	Variants No.	Variants %
86F212	8	0	0	3	38
86F214	8	0	0	5	63
86F218	10	0	0	1	10
86F231	12	0	0	5	42
86F235	10	0	0	3	30
86F236	8	0	0	5	63
86F237	8	0	0	3	38
86F297	9	0	0	7	78
86F303	8	0	0	2	25
86F304	10	0	0	1	10
86F309	10	0	0	9	90
86F316	11	0	0	0	0
86F321	9	0	0	2	22

Appendix O(Cont.)

INCIDENCE OF FETAL MALFORMATIONS AND VARIATIONS

100 mg/kg/day Nitroguanidine Animals

Maternal ID	Number Examined	Malformed No.	Malformed %	Variants No.	Variants %
86F202	7	0	0	0	0
86F203	9	0	0	5	56
86F210	9	0	0	0	0
86F225	9	0	0	9	100
86F226	6	0	0	2	33
86F230	6	0	0	1	17
86F232	11	0	0	11	100
86F239	10	0	0	4	40
86F292	11	0	0	3	27
86F295	8	0	0	1	13
86F300	10	0	0	2	20
86F308	10	1	10	7	70
86F310	10	0	0	7	70
86F311	10	0	0	7	70
86F320	9	0	0	6	67

Appendix O(Cont.)

INCIDENCE OF FETAL MALFORMATIONS AND VARIATIONS

316 mg/kg/day Nitroguanidine Animals

Maternal ID	Number Examined	Malformed No.	Malformed %	Variants No.	Variants %
86F215	7	0	0	0	0
86F217	11	0	0	6	55
86F220	9	0	0	4	44
86F223	10	0	0	10	100
86F224	12	0	0	11	92
86F227	9	0	0	1	11
86F234	9	0	0	3	33
86F238	8	0	0	2	25
86F284	8	0	0	3	38
86F285	7	0	0	2	29
86F298	10	0	0	2	20
86F301	9	0	0	5	56
86F313	8	0	0	5	63
86F314	3	0	0	3	100
86F322	11	0	0	5	45

Appendix O(Cont.)

INCIDENCE OF FETAL MALFORMATIONS AND VARIATIONS

1000 mg/kg/day Nitroguanidine Animals

Maternal ID	Number Examined	Malformed No.	Malformed %	Variants No.	Variants %
86F221	9	0	0	5	56
86F228	9	0	0	9	100
86F240	10	0	0	3	30
86F283	11	0	0	4	36
86F288	9	0	0	7	78
86F294	6	0	0	6	100
86F296	10	0	0	4	40
86F302	4	0	0	1	25
86F312	11	0	0	5	45
86F317	8	1	13	8	100

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Alexandria, VA 22304-6145

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